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APPLICATION NUMBER: ***10/662,613***
FILING DATE: ***September 15, 2003***

CA/04/1674

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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	P05562US00
First Inventor	FARID, Abdol Hossain, et al.
Title	INSULIN-LIKE GROWTH FACTOR-1
Express Mail Label No.	EV 330573076 US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Mail Stop Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

03940 U.S. PTO
10/662613
09/15/03

1. ☑ Fee Transmittal Form (e.g., PTO/SB/17)
(Submit an original and a duplicate for fee processing)
2. ☐ Applicant claims small entity status.
See 37 CFR 1.27.
3. ☑ Specification [*Total Pages* 72]
(preferred arrangement set forth below)
- Descriptive title of the invention
- Cross Reference to Related Applications
- Statement Regarding Fed sponsored R & D
- Reference to sequence listing, a table, or a computer program listing appendix
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings *(if filed)*
- Detailed Description
- Claim(s)
- Abstract of the Disclosure

4. ☑ Drawing(s) (*35 U.S.C. 113*) [*Total Sheets* 83]
5. Oath or Declaration [*Total Sheets* _____]
a. ☐ Newly executed (original or copy)
b. ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional with Box 18 completed)
i. ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) name in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. ☑ Application Data Sheet. See 37 CFR 1.76
7. ☐ CD-ROM or CD-R in duplicate, large table or Computer Program *(Appendix)*
8. Nucleotide and/or Amino Acid Sequence Submission
(if applicable, all necessary)
a. ☑ Computer Reader Form (CRF)
b. Specification Sequence Listing on:
i. ☐ CD-ROM or CD-R (2 copies); or
ii. ☑ Paper
c. ☑ Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

9. ☐ Assignment Papers (cover sheet & document(s))
10. ☐ 37 CFR 3.73(b) Statement ☐ Power of Attorney
(when there is an assignee)
11. ☐ English Translation Document *(if applicable)*
12. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
13. ☐ Preliminary Amendment
14. ☑ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
15. ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)
16. ☐ Nonpublication Request under 35 U.S.C. 122 (b)(2)(B)(i). Applicant must attach form PTO/SB/35 or its equivalent.
17. ☐ Other: .....

18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: .....

Prior application information: *Examiner* _____ *Art Unit:* _____

For CONTINUATION OF DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

19. CORRESPONDENCE ADDRESS

☑ Customer Number: 22885 *OR* ☐ Correspondence address below

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Name (Print/Type)	HEIDI GRASE NEBEL	*Registration No. (Attorney/Agent)*	37,719
Signature		*Date*	9/15/03

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FEE TRANSMITTAL for FY 2003

Effective 01/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 2,250.00

Complete if Known	
Application Number	
Filing Date	
First Named Inventor	FARID, Abdol Hossain, et al.
Examiner Name	
Art Unit	
Attorney Docket No.	P05562US00

METHOD OF PAYMENT *(check all that apply)*

☑ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 26-0084

Deposit Account Name: McKee, Voorhees & Sease, P.L.C.

The Director is authorized to: *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) during the pendency of this application

☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	750	2001	375	Utility filing fee	750.00
1002	330	2002	165	Design filing fee	
1003	520	2003	260	Plant filing fee	
1004	750	2004	375	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 750.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below		Fee Paid
Total Claims	80	-20** =	60	X	18	=	1080.
Independent Claims	8	-3** =	5	X	84	=	420.
Multiple Dependent						=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	84	2201	42	Independent claims in excess of 3
1203	280	2203	140	Multiple dependent claim, if not paid
1204	84	2204	42	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 1,500.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	410	2252	205	Extension for reply within second month	
1253	930	2253	465	Extension for reply within third month	
1254	1,450	2254	725	Extension for reply within fourth month	
1255	1,970	2255	985	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,300	2453	650	Petition to revive - unintentional	
1501	1,300	2501	650	Utility issue fee (or reissue)	
1502	470	2502	235	Design issue fee	
1503	630	2503	315	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	750	2809	375	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	750	2810	375	For each additional invention to be examined (37 CFR 1.129(b))	
1801	750	2801	375	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($) 0

SUBMITTED BY					(Complete *if applicable*)	
Name (Print/Type)	HEIDI SEASE NEBEL	*Registration No. (Attorney/Agent)*	37,719	*Telephone*	515-288-3667	
Signature				*Date*	9/18/03	

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If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

TITLE: INSULIN-LIKE GROWTH FACTOR-1 RECEPTOR (IGF-1R) POLYMORPHIC ALLELES AND USE OF THE SAME TO IDENTIFY DNA MARKERS FOR REPRODUCTIVE LONGEVITY

BACKGROUND OF THE INVENTION

Genetic mutations are the basis of evolution and genetic diversity. Genetic markers represent specific loci in the genome of a species, population or closely related species, and sampling of different genotypes at these marker loci reveals genetic variation. The genetic variation at marker loci can then be described and applied to genetic studies, commercial breeding, diagnostics, and cladistics. Genetic markers have the greatest utility when they are codominant, highly heritable, multi-allelic, and numerous. Most genetic markers are heritable because their alleles are determined by the nucleotide sequence of DNA which is highly conserved from one generation to the next, and the detection of their alleles is unaffected by the natural environment. Markers have multiple alleles because, in the evolutionary process, rare, genetically–stable mutations in DNA sequences defining marker loci arose and were disseminated through the generations along with other existing alleles. The highly conserved nature of DNA combined with rare occurrences of stable mutations allows genetic markers to be both predictable and discerning of different genotypes. The repertoire of genetic-marker technologies today allows multiple technologies to be used simultaneously in the same project. The invention of each new genetic-marker technology and each new DNA polymorphism adds additional utility to genetic markers. Many genetic-marker technologies exist. Some examples are restriction-fragment-length polymorphism (RFLP) Bostein et al (1980) *Am J Hum Genet* 32:314-331; single-strand conformation polymorphism (SSCP) Fischer et al. (1983) *Proc Natl Acad Sci USA* 80:1579-1583, Orita et al. (1989) *Genomics* 5:874-879; amplified fragment-length polymorphism (AFLP) Vos et al. (1995) *Nucleic Acids Res* 23:4407-4414; microsatellite or single-sequence repeat (SSR) Weber J L and May P E (1989) *Am J Hum Genet* 44:388-396; random-amplified polymorphic DNA (RAPD) Williams et al (1990) *Nucleic Acids Res* 18:6531-6535; sequence tagged site (STS) Olson et al. (1989) *Science* 245:1434-1435; genetic-bit analysis (GBA) Nikiforov et al (1994) *Nucleic Acids Res* 22:4167-4175; allele-specific polymerase chain reaction (ASPCR) Gibbs et al. (1989) *Nucleic Acids* Res 17:2437-2448, Newton et al. (1989) *Nucleic Acids Res* 17:2503-2516; nick-translation

PCR (e.g., TAQMAN™) Lee et al. (1993) *Nucleic Acids Res* 21:3761-3766; and allele-specific hybridization (ASH) Wallace et al. (1979) *Nucleic Acids Res* 6:3543-3557, (Sheldon et al. (1993) *Clinical Chemistry* 39(4):718-719) among others. Each technology has its own particular basis for detecting polymorphisms in DNA sequence.

The ability to follow a specific favorable genetic allele involves a novel and lengthy process of the identification of a DNA molecular marker for a major effect gene. The marker may be linked to a single gene with a major effect or linked to a number of genes with additive effects. DNA markers have several advantages; segregation is easy to measure and is unambiguous, and DNA markers are co-dominant, i.e., heterozygous and homozygous animals can be distinctively identified. Once a marker system is established selection decisions could be made very easily, since DNA markers can be assayed any time after a tissue or blood sample can be collected from the individual infant animal, or even an embryo.

Poor reproductive performance is one of the major causes for culling in dairy (Beaudeau et al. 1995; Durr et al. 1997; Kulak et al. 1997; Bascom and Young 1998) and beef cattle (Tanida et al. 1988), and leads to a decrease in profitability (Tanida et al. 1988; Beaudeau et al. 1995; Kulak et al. 1997; Bascom and Young 1998). The highest level of profitability in a dairy herd is achieved when high yielding cows are maintained in the herd for several lactations (Gill and Allaire 1976; Allaire and Gibson 1992; Kulak et al. 1997). An increase in length of production from 3 to 4 lactations increases milk yield per lactation and profit per year by 11 and 13% respectively (Strandberg 1996). Reproductive longevity is even more important in beef cattle, sheep, swine and fur bearing animals, where replacement cost is, after nutrition, the second highest source of expenditure. Clearly, improving reproductive longevity offers one of the greatest opportunities for increasing productive efficiency and economic return in the multi-billion dollar livestock industry in the world. This is illustrated by the fact that reproductive longevity is included in the national dairy genetic evaluation systems in Canada (herd life) and the U.S. (production life).

Moderate variation exists for reproductive longevity within and among different breeds of cattle (Silva et al. 1986; Smith and Quass 1984; Bailey 1991; Arthur et al. 1993), suggesting the possibility for genetic improvement in this trait. However, despite its

obvious economic importance, it is difficult to improve reproductive longevity through conventional breeding methods because of the low heritability of this trait (Smith and Quass 1984; Tanida et al. 1988; Boldman et al. 1992; VanRaden and Klaaskate 1993) and the long time necessary to obtain information on reproductive longevity in livestock. Attempts to improve reproductive longevity of dairy cattle through indirect selection, such as the use of 'type traits' that are measured early in life, has been ineffective (Smith and Quass 1984; Boldman et al. 1992; VanRaden and Klasskate 1993).

The above limitations make reproductive longevity an ideal candidate trait for the use of DNA markers (Lande and Thompson 1990), which would provide a means of identification of animals with superior breeding value at an early age on the basis of a simple laboratory test. Developing DNA markers for reproductive longevity is, however, a difficult and time-consuming task in long-lived livestock resources. A logical strategy would involve identification of candidate genes in a mammalian model with a short generation interval and later validating them in livestock (Copeland et al. 1993). This is especially true in the case of genes that control reproductive longevity and life span (Rose and Nusbaum 1994), since direct selection for prolonged reproductive age in large mammals is very time consuming and prohibitively expensive. The genes identified in animals will be putative candidates for the development of DNA markers for reproductive longevity in other species.

Although there are several reports on the quantitative genetics aspects of reproductive longevity in livestock (VanRaden and Klaaskate 1993; Smith and Quass 1984; Kulak *et al.* 1997; Bascom and Young 1998), little information is available on the genetic control of this trait in any mammalian species. Most of the available information on the genetic control of reproductive longevity and life span has been obtained on simple organisms, such as *Drosophila* and *Caenorhabditis elegans* (*C. elegans*). In *C. elegans*, for example, the *daf* genes (*daf-2, -12, -16, -18 -23*), which are components of the IGF-1R signaling cascade, have been shown to control the regulation of metabolism, development, reproduction and life span (Lakowski and Hekimi 1996; Apfeld and Kenyon 1998; Hekimi *et al.* 1998). Also, there is a positive relationship between life span and reproduction in *C. elegans* (Hsin and Kenyon 1999) and among mammals (Packer et *al.* 1998; Tissenbaum and Ruvkun 1998). Although information on lower organisms is useful, their usefulness in

mammals should be assessed in an appropriate mammalian model that exhibits widely contrasting reproductive longevity phenotypes.

The use of DNA markers will facilitate the identification of animals that are genetically prone to a) reproduce longer than the average and, separately b) those that have a higher likelihood, compared with the average, of conceiving during lactation (sustained lactation and pregnancy stress). The marker may be directly involved in prolonging reproductive life, or may be linked to a single gene with a major effect, or may be linked to a number of genes with additive effects on animals' phenotype. Their segregation is easy to measure and is unambiguous, and DNA markers are co-dominant, i.e., heterozygous and homozygous animals can be distinctively identified. Once a marker system is established, selection decisions can be made easily, since DNA markers can be assayed any time after a tissue or blood sample can be collected from the individual infant animal, or even an embryo.

For the foregoing reasons, there is a need for a method of selecting animals with improved reproductive longevity and/or ability to better sustain stress factors. More particularly, a need for identifying markers which may be used to improve economically beneficial characteristics in animals by identifying and selecting animals with these favorable characteristics at the genetic level.

Therefore, an object of the present invention is to provide a method of identifying polymorphisms in the IGF-1R gene which are indicative of reproductive longevity in mammals and their ability to sustain performance in combination with stress factors such as lactation, pregnancy, and health status.

Another object of the invention is to provide assays for determining the presence of these genetic markers.

A further object of the invention is to provide methods for screening animals to determine those more likely to exhibit favorable traits associated with reproductive longevity and the ability to sustain performance under stress, which increases the accuracy of selection and breeding methods.

Yet another object of the invention is to provide PCR amplification and detection tests which will greatly expedite the determination of presence of the markers.

A still further object of the invention is to provide a method for determining the haplotype of the IGF-1R gene indicative of reproductive longevity and the ability to sustain performance under stress.

Additional objects and advantages of the invention will be set forth in part in the description that follows, and in part will be obvious from the description, or may be learned by the practice of the invention. The objects and advantages of the invention will be attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

BRIEF SUMMARY OF THE INVENTION

This invention relates to the discovery of alternate forms of the insulin-like growth factor-1 receptor (IGF-1R) gene which are useful as a genetic markers associated with reproductive longevity and the ability to better sustain stress factors in animals such as lactation and pregnancy in animals.

According to an embodiment of the present invention there are provided methods for identifying a polymorphism in an animal. One embodiment includes a method for genetically identifying an animal comprising obtaining a sample of genetic material from an animal and assaying for the presence of a polymorphism in the insulin-like growth factor 1 receptor gene (IGF-1R), wherein said polymorphism is associated with reproductive longevity and/or ability to better sustain stress factors such as lactation and pregnancy stress.

A further embodiment includes a method for screening animals to determine those more likely to exhibit favorable traits associated with reproductive longevity and ability to sustain stress factors such as lactation and pregnancy stress. These methods include obtaining a genetic sample from the animal. The methods can further include assaying for the presence or absence of a polymorphism in the IGF-1R gene associated with reproductive longevity and/or the ability to sustain stress factors in animals such as lactation and pregnancy.

Further embodiments of the invention can include amplifying the gene or a region of the gene, which contains at least one polymorphism. Since one of the polymorphisms may involve changes in the amino acid composition of the IGF-1R protein, assay methods

may even involve ascertaining the amino acid composition of these proteins. Methods for this type or purification and analysis typically involve isolation of the protein through means including fluorescence tagging with antibodies, separation and purification of the protein (i.e., through reverse phase HPLC system), and use of an automated protein sequencer to identify the amino acid sequence present. Protocols for this assay are standard and known in the art and are disclosed in Ausubel et al. (eds.), *Short Protocols in Molecular Biology* 4th ed. (John Wiley and Sons 1999).

Another embodiment includes a method for determining the haplotype of the IGF-1R gene of an animal wherein the haplotype is indicative of reproductive longevity and/or ability to sustain stress factors.

In a preferred embodiment, a sample of genetic material is obtained from an animal and the sample is analyzed to determine the presence or absence of a polymorphism in the IGF-1R gene, which is correlated with reproductive longevity and/or ability to sustain stress factors such as lactation and pregnancy stress.

As is well known to those of skill in this art, a variety of techniques may be utilized when comparing nucleic acid molecules for sequence differences. These include by way of example, restriction fragment length polymorphism analysis, heteroduplex analysis, single-strand conformation polymorphism analysis, denaturing gradient electrophoresis and temperature gradient electrophoresis.

In a preferred embodiment the polymorphism is a 12-bp deletion and two restriction fragment length polymorphism and the assay comprises identifying the animal's IGF-1R gene from isolated genetic material; exposing the gene to a restriction enzyme that yields restriction fragments of the gene of varying length; separating the restriction fragments to form a restriction pattern, such as by electrophoresis or HPLC separation; and comparing the resulting restriction fragment pattern from a IGF-1R gene that is either known to have or not to have the desired marker.

In a most preferred embodiment the gene is isolated by the use of primers and DNA polymerase to amplify a specific region of the gene which contains the polymorphism. Next the amplified region is digested with a restriction enzyme and fragments are again separated. Visualization of the RFLP pattern is by simple staining of the fragments, or by labeling the primers or the nucleoside triphosphates used in amplification.

It expected that with no more than routine testing as described herein this marker can be applied to different animal species to select for reproductive longevity and/or sustained performance in a situation with stress caused by lactation, pregnancy, or health status based on the teachings herein. Female animals of the same breed or breed cross or similar genetic lineage are bred, and the reproductive longevity and/or sustained lactation and pregnancy stress shown by each animal is determined and correlated. For other species in which sequences are available a BLAST comparison of the IGF-1R may be used to ascertain whether the particular allele disclosed herein is present.

The term "analogous polymorphism" shall be a polymorphism which is the same as any of those disclosed herein as determined by BLAST comparisons.

The following terms are used to describe the sequence relationships between two or more nucleic acids or polynucleotides: (a) "reference sequence", (b) "comparison window", (c) "sequence identity", (d) "percentage of sequence identity", and (e) "substantial identity".

(a) As used herein, "reference sequence" is a defined sequence used as a basis for sequence comparison. In this case the Reference is the IGF-1R sequence. A reference sequence may be a subset or the entirety of a specified sequence; for example, as a segment of a full-length cDNA or gene sequence, or the complete cDNA or gene sequence.

(b) As used herein, "comparison window" includes reference to a contiguous and specified segment of a polynucleotide sequence, wherein the polynucleotide sequence may be compared to a reference sequence and wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (i.e., gaps) compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Generally, the comparison window is at least 20 contiguous nucleotides in length, and optionally can be 30, 40, 50, 100, or longer. Those of skill in the art understand that to avoid a high similarity to a reference sequence due to inclusion of gaps in the polynucleotide sequence, a gap penalty is typically introduced and is subtracted from the number of matches.

Methods of alignment of sequences for comparison are well-known in the art. Optimal alignment of sequences for comparison may be conducted by the local homology algorithm of Smith and Waterman, *Adv. Appl. Math.* 2:482 (1981); by the homology alignment algorithm of Needleman and Wunsch, *J. Mol. Biol.* 48:443 (1970); by the search

for similarity method of Pearson and Lipman, *Proc. Natl. Acad. Sci.* 85:2444 (1988); by computerized implementations of these algorithms, including, but not limited to: CLUSTAL in the PC/Gene program by Intelligenetics, Mountain View, California; GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, Wisconsin, USA; the CLUSTAL program is well described by Higgins and Sharp, *Gene* 73:237-244 (1988); Higgins and Sharp, CABIOS 5:151-153 (1989); Corpet, et al., *Nucleic Acids Research* 16:10881-90 (1988); Huang, *et al., Computer Applications in the Biosciences* 8:155-65 (1992), and Pearson, *et al., Methods in Molecular Biology* 24:307-331 (1994). The BLAST family of programs which can be used for database similarity searches includes: BLASTN for nucleotide query sequences against nucleotide database sequences; BLASTX for nucleotide query sequences against protein database sequences; BLASTP for protein query sequences against protein database sequences; TBLASTN for protein query sequences against nucleotide database sequences; and TBLASTX for nucleotide query sequences against nucleotide database sequences. See, *Current Protocols in Molecular Biology*, Chapter 19, Ausubel, et al., Eds., Greene Publishing and Wiley-Interscience, New York (1995).

Unless otherwise stated, sequence identity/similarity values provided herein refer to the value obtained using the BLAST 2.0 suite of programs using default parameters. Altschul et al., *Nucleic Acids Res.* 25:3389-3402 (1997). Software for performing BLAST analyses is publicly available, e.g., through the National Center for Biotechnology-Information (http://www.ncbi.nlm.nih.gov/).

This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul et al., *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues;

always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, a cutoff of 100, M=5, N=-4, and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength (W) of 3, an expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff & Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915).

In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin & Altschul, *Proc. Natl. Acad. Sci. USA* 90:5873-5787 (1993)). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance.

BLAST searches assume that proteins can be modeled as random sequences. However, many real proteins comprise regions of nonrandom sequences which may be homopolymeric tracts, short-period repeats, or regions enriched in one or more amino acids. Such low-complexity regions may be aligned between unrelated proteins even though other regions of the protein are entirely dissimilar. A number of low-complexity filter programs can be employed to reduce such low-complexity alignments. For example, the SEG (Wooten and Federhen, *Comput. Chem.*, 17:149-163 (1993)) and XNU (Claverie and States, *Comput. Chem.*, 17:191-201 (1993)) low-complexity filters can be employed alone or in combination.

(c) As used herein, "sequence identity" or "identity" in the context of two nucleic acid or polypeptide sequences includes reference to the residues in the two sequences which are the same when aligned for maximum correspondence over a specified comparison window. When percentage of sequence identity is used in reference to proteins it is recognized that residue positions which are not identical often differ by conservative

amino acid substitutions, where amino acid residues are substituted for other amino acid residues with similar chemical properties (e.g. charge or hydrophobicity) and therefore do not change the functional properties of the molecule. Where sequences differ in conservative substitutions, the percent sequence identity may be adjusted upwards to correct for the conservative nature of the substitution. Sequences which differ by such conservative substitutions are said to have "sequence similarity" or "similarity". Means for making this adjustment are well-known to those of skill in the art. Typically this involves scoring a conservative substitution as a partial rather than a full mismatch, thereby increasing the percentage sequence identity. Thus, for example, where an identical amino acid is given a score of 1 and a non-conservative substitution is given a score of zero, a conservative substitution is given a score between zero and 1. The scoring of conservative substitutions is calculated, e.g., according to the algorithm of Meyers and Miller, *Computer Applic. Biol. Sci.*, 4:11-17 (1988) e.g., as implemented in the program PC/GENE (Intelligenetics, Mountain View, California, USA).

(d) As used herein, "percentage of sequence identity" means the value determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (i.e., gaps) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity.

(e) The term "substantial identity" of polynucleotide sequences means that a polynucleotide comprises a sequence that has at least 70% sequence identity, preferably at least 80%, more preferably at least 90% and most preferably at least 95%, compared to a reference sequence using one of the alignment programs described using standard parameters. One of skill will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and

the like. Substantial identity of amino acid sequences for these purposes normally means sequence identity of at least 60%, or preferably at least 70%, 80%, 90%, and most preferably at least 95%.

These programs and algorithms can ascertain the analogy of a particular polymorphism in a target gene to those disclosed herein. It is expected that this polymorphism will exist in other animals and use of the same in other animals than disclosed herein involved no more than routine optimization of parameters using the teachings herein.

It is also possible to establish linkage between specific alleles of alternative DNA markers and alleles of DNA markers known to be associated with a particular gene (e.g. the IGF-1R gene discussed herein), which have previously been shown to be associated with a particular trait. Thus, in the present situation, taking the IGF-1R gene, it would be possible, at least in the short term, to select for animals likely to produce one or more of the traits of reproductive longevity and/or the ability to better sustain stress caused by lactation and pregnancy, or alternatively against animals less likely to exhibit the traits of reproductive longevity and/or the ability to better sustain stress caused by lactation and pregnancy, indirectly, by selecting for certain alleles of a IGF-1R associated marker through the selection of specific alleles of alternative chromosome markers. As used herein the term "genetic marker" shall include not only the polymorphism disclosed by any means of assaying for the protein changes associated with the polymorphism, be they linked markers, use of microsatellites, or even other means of assaying for the causative protein changes indicated by the marker and the use of the same to influence the traits of reproductive longevity and/or the ability to sustain stress in an animal.

As used herein, often the designation of a particular polymorphism is made by the name of a particular restriction enzyme. This is not intended to imply that the only way that the site can be identified is by the use of that restriction enzyme. There are numerous databases and resources available to those of skill in the art to identify other restriction enzymes which can be used to identify a particular polymorphism. Two examples are: http://www.geneseo.edu/~bio/ and http://www.firstmarket.com/cutter/cut2.html. In fact, as disclosed in the teachings herein there are numerous ways of identifying a particular

polymorphism or allele with alternate methods which may not even include a restriction enzyme, but which assay for the same genetic or proteomic alternative form.

The invention is intended to include these sequences as well as all conservatively modified variants thereof as well as those sequences which will hybridize under conditions of high stringency to the sequences disclosed. The term IGF-1R is used herein shall be interpreted to include these conservatively modified variants as well as those hybridized sequences.

The term "conservatively modified variants" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refer to those nucleic acids which encode identical or conservatively modified variants of the amino acid sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations" and represent one species of conservatively modified variation. Every nucleic acid sequence herein that encodes a polypeptide also, by reference to the genetic code, describes every possible silent variation of the nucleic acid. One of ordinary skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine; and UGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide of the present invention is implicit in each described polypeptide sequence and is within the scope of the present invention.

As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Thus, any number of amino acid residues selected from the group of integers consisting of from 1 to 15 can be so altered. Thus, for example, 1, 2, 3, 4, 5, 7, or 10 alterations can be made.

Conservatively modified variants typically provide similar biological activity as the unmodified polypeptide sequence from which they are derived. For example, substrate specificity, enzyme activity, or ligand/receptor binding is generally at least 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the native protein for its native substrate. Conservative substitution tables providing functionally similar amino acids are well known in the art.

The following six groups each contain amino acids that are conservative substitutions for one another:

1) Alanine (A), Serine (S), Threonine (T);
2) Aspartic acid (D), Glutamic acid (E);
3) Asparagine (N), Glutamine (Q);
4) Arginine (R), Lysine (K);
5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and
6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

See also, Creighton, *Proteins*, W.H. Freeman and Company (1984).

By "encoding" or "encoded", with respect to a specified nucleic acid, is meant comprising the information for translation into the specified protein. A nucleic acid encoding a protein may comprise non-translated sequences (e.g., introns) within translated regions of the nucleic acid, or may lack such intervening non-translated sequences (e.g., as in cDNA). The information by which a protein is encoded is specified by the use of codons. Typically, the amino acid sequence is encoded by the nucleic acid using the "universal" genetic code. However, variants of the universal code, such as are present in some plant, animal, and fungal mitochondria, the bacterium *Mycoplasma capricolum*, or the ciliate *Macronucleus*, may be used when the nucleic acid is expressed therein.

The term "stringent conditions" or "stringent hybridization conditions" includes reference to conditions under which a probe will hybridize to its target sequence, to a detectably greater degree than to other sequences (e.g., at least 2-fold over background). Stringent conditions are sequence-dependent and be different in different circumstances. By controlling the stringency of the hybridization and/or washing conditions, target sequences can be identified which are 100% complementary to the probe (homologous probing). Alternatively, stringency conditions can be adjusted to allow some mismatching in sequences so that lower degrees of similarity are detected (heterologous probing).

Generally, a probe is less than about 1000 nucleotides in length, optionally less than 500 nucleotides in length.

Typically, stringent conditions will be those in which the salt concentration is less than about 1.5 M Na ion, typically about 0.01 to 1.0 M Na ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes (*e.g.*, 10 to 50 nucleotides) and at least about 60°C for long probes (*e.g.*, greater than 50 nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide. One of ordinary skill is apprised in knowing that the time of the hybridization is dependent on the concentration of the probe. Exemplary low stringency conditions include hybridization with a buffer solution of 30 to 35% formamide, 1 M NaCl, 1% SDS (sodium dodecyl sulphate) at 37°C, and a wash in 1X to 2X SSC (20X SSC = 3.0 M NaCl/0.3 M trisodium citrate) at 50 to 55°C. Exemplary moderate stringency conditions include hybridization in 40 to 45% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 0.5X to 1X SSC at 55 to 50°C. Exemplary high stringency conditions include hybridization in 50% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 0.1X SSC at 60 to 65°C for at least 15 minutes.

Specificity is typically the function of post-hybridization washes, the critical factors being the ionic strength and temperature of the final wash solution. For DNA-DNA hybrids, the T_m can be approximated from the equation of Meinkoth and Wahl, *Anal. Biochem.*, 138:267-284 (1984): T_m=81.5°C + 16.6 (log M) + 0.41 (%GC) –0.61 (% form) – 500/L; where M is the molarity of monovalent cations, %GC is the percentage of guanosine and cytosine nucleotides in the DNA, % form is the percentage of formamide in the hybridization solution, and L is the length of the hybrid in base pairs. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the complementary target sequence hybridizes to a perfectly matched probe. T_m is reduced by about 1°C for each 1% of mismatching; thus, T_m, hybridization and/or wash conditions can be adjusted to hybridize to sequences of the desired identity. For example, if sequences with ≥90% identity are sought, the T_m can be decreased 10°C. Generally, stringent conditions are selected to be about 5°C lower than the thermal melting point (T_m) for the specific sequence and its complement at a defined ionic strength and pH. However, severely stringent conditions can utilize a hybridization and/or wash at 1, 2, 3, or 4°C lower than the

thermal melting point (T_m); moderately stringent conditions can utilize a hybridization and/or wash at 6, 7, 8, 9, or 10°C lower than the thermal melting point (T_m); low stringency conditions can utilize a hybridization and/or wash at 11, 12, 13, 14, 15, or 20°C lower than the thermal melting point (T_m). Using the equation, hybridization and wash compositions, and desired T_m, those of ordinary skill will understand that variations in the stringency of hybridization and/or wash solutions are inherently described. If the desired degree of mismatching results in a T_m of less than 45°C (aqueous solution) or 32°C (formamide solution) it is preferred to increase the SSC concentration so that a higher temperature can be used. An extensive guide to the hybridization of nucleic acids is found in Tijssen, *Laboratory Techniques in Biochemistry and Molecular Biology—Hybridization with Nucleic Acids Probes*, Part I, Chapter 2, Ausubel, *et al.*, Eds., Greene Publishing and Wiley-Interscience, New York (1995).

These and other features, aspects, and advantages of the present invention will become better understood with regard to the following description, appended claims, and accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the nucleotide sequence of the insulin-like growth factor-1 receptor in mice (SEQ ID NO:1)(GenBank accession number AF056187).

Figure 2 depicts the amino acid sequence of the insulin-like growth factor-1 receptor in mice (SEQ ID NO:2)(GenBank protein id AAC12782.1).

Figure 3 depicts the mRNA sequence of insulin-like growth factor I receptor in mice (SEQ ID NO:3) (Genbank accession number XM_133508).

Figure 4 depicts the alignment of exon 21 of the mouse IGF1-R sequences from Genbank accession number AF056187 (SEQ ID NO: 1) and Genbank accession number XM_133508 (SEQ ID NO:3), and the amino acid sequence of this region (SEQ ID NO:4). The A to G substitution at position 3876 of the Genbank accession number AF056187 (*HpaII* site, locus B) is bolded and underlined. The 12 bp insertion/deletion is bolded and underlined. The junction of exon 20 and exon 21 is shown by "0".

Figure 5 depicts intron 16 (SEQ ID NO:5) of the mouse IGF1-R gene and the surrounding exons amplified by primers PSEQ16F (SEQ ID NO:12) and PSEQ16R (SEQ

ID NO:13), and its alignment with the mouse IGF1-R gene (Genbank accession number AC101879; SEQ ID NO:6). This sequence contains 102 bp of exon 16 (nucleotides 1 to 102), 283 bp of intron 16 (nucleotides 103 to 385) and 101 bp of exon 17 (nucleotides 386 to 486) of the mouse IFG1-R gene. Exon-intron junctions are shown by 0. The 'G' insertion is at position 176 of SEQ ID NO:5 after nucleotide 56456 of SEQ ID NO:6 (Genbank accession number AC101879). This insertion is bolded and underlined. Note that SEQ ID NO:6 (Genbank accession number AC101879) is the reverse complement of other sequences of the IGF1-R in Genbank. The 'G' to 'A' substitution (*DpnII* site, locus A) is at position 331 of SEQ ID NO:5, corresponding to nucleotide 556303 of SEQ ID NO:6 (Genbank accession number AC101879). This nucleotide is bolded and underlined. The forward (PSEQ16F) and reverse (PSEQ16R) primers are underlined.

Figure 6 depicts mouse clone RP23-378H21, complete sequence (SEQ ID NO:6) (Genbank accession number AC101879).

Figure 7 depicts the nucleotide sequence of the insulin-like growth factor-1 receptor in pig (SEQ ID NO:7). cDNA sequence in lower case letters comes from Accession No. AB003362. Intron 9 sequence in lower case letters comes from Accession No. AJ491314. Intron sequence in upper case letters was derived from Applicants sequencing efforts.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Unless mentioned otherwise, the techniques employed or contemplated herein are standard methodologies well known to one of ordinary skill in the art.

As used herein, "reproductive longevity" means a biologically significant increase in the number of pregnancies and/or the duration of time an animal is capable of reproduction, relative to the mean of a given population, group or species.

As used herein, "the ability to sustain performance under stress" means a biologically significant increase in performance, in situations with stress, i.e., increase in the number of pregnancies and/or the duration of time while the animal is lactating and raising progeny, i.e., carrying a fetus while lactating at the same time, relative to the mean of a given population.

The insulin-like growth factor-1 receptor (IGF-1R) gene is a plasma membrane-bound disulfide-bonded heterotetrameric glycoprotein composed of two extracellular α-subunits containing a ligand binding domain and two transmembrane β-subunits that include a cytoplasmic tyrosine kinase domain (Richards et al., 1998). The IGF-1R gene plays a vital role in growth and development in several different ways, such as mediating mitogenic and metabolic responses, maintaining transformed cell phenotype, protecting cells from apoptotic injuries, and inducing differentiation in certain cell types especially myoblasts, adipocytes, osteoblasts and cells of the central nervous system (Valentinis et al., 1999; Jin et al., 2000).

Binding of the ligand to IGF-1R leads to autophosphorylation of the α-subunit and activation of the β-subunit tyrosine kinase domains resulting in phosphorylation of several intracellular proteins including insulin receptor substrates (IRS) and Shc with the subsequent trigger of multiple signaling cascades, for instance those of the Ras-Raf-MAP kinase network and phosphatidylinositol 3-kinase. The various effects may depend on specific domains of the receptor and the availability of different substrates (Peruzzi et al., 1999; Swantek et al., 1999; Valentinis et al., 1999; Xu et al., 1999; Soni et al.; 2000).

The IGF-1R gene also plays a role in certain functions of other growth factors and hormones. There is evidence that a signal generated by a functional IGF-1R is required for the mitogenic effects of other growth factors, such as epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) (Swantek and Baserga, 1999). Furthermore, the estradiol-induced mitogenic effects in the mouse uterus and differentiation of rat adipocytes are dependent on the IGF-1R (Richards et al., 1998; Dieudonne et al., 2000).

According to an embodiment of the present invention variants or polymorphic sites in the IGF-1R gene have been located, and these genetic polymorphisms are associated with reproductive longevity and/or the ability the sustain stress factors such as lactation and pregnancy in mice. These four variants include an 'A' to 'G' substitution in intron 16, a 'G' nucleotide insertion in intron 16, an 'A' to 'G' substitution in exon 21, and a 12 bp-deletion in exon 21 which resulted in four fewer amino acids in the IGF-1R protein.

In another embodiment, assays are provided for detection of these different variants. The assays preferably involve amplifying the genomic DNA purified from blood, tissue,

semen, or other convenient source of genetic material by the use of primers and standard techniques, such as polymerase chain reaction (PCR).

A 12 bp deletion, PCR product was identified in mice. The PCR product can be sized in a variety of ways, such as by agarose or polyacrylamide gel electrophoresis, use of an automated DNA sequencer, or mass spectrometry.

An 'A' to 'G' substitution, at position 3876 of SEQ ID NO:1 (Genbank accession number AF056187) was identified in mice. The PCR product was digested with a restriction enzyme (e.g., *HpaII*) so as to yield gene fragments of varying lengths, as separating at least some of the fragments from others using agarose or polyacrylamide gel electrophoresis. Since the 'A' to 'G' substitution is 20 base pairs upstream from the 12-base pair deletion, both polymorphisms may be detected by the digestion of PCR product with the enzyme *HpaII*.

A 'G' to 'A' substitution (GGTC to GATC) was detected in intron 16 of the gene in mice. The 486 bp PCR product, spanning exons 16 and 17 and intron 16, was cut into 454 and 32 bp fragments (A_1 allele) by the enzyme *DpnII* (↑GATC). This nucleotide substitution resulted in the creation of a new recognition site for this enzyme, which cleaved the 454 bp fragment into 328 and 125 bp fragments (A_2 allele). In addition, sequence information revealed a 'G' nucleotide insertion in intron 16, 153 bp 5′ to the above point mutation, but no restriction enzyme was found for discriminatory typing of this deletion.

In porcine, the following single nucleotide polymorphisms were found:

A 'G' to 'A' substitution, designated SNP16i27, at position 27 from the end of intron 16 was detected with an *AvaII* restriction site.

A 'G' to 'C' substitution, designated SNP16i73, was detected at position 73 from the end of intron 16. This nucleotide substitution resulted in a *MnlI* restriction site.

A 'G' to 'A' substitution, designated SNP1772, was detected in exon 8. This nucleotide substitution resulted in a *TaqI* restriction site.

The polymorphisms in animals may also be identified using a variety of methods such as direct sequencing, and hybridizing with nucleotide probes labeled with radioactive or chemiluminescence. The probes may be sequences containing all or a portion of the IGF-1R gene containing the polymorphisms, which will be hybridized to the separated

digestion PCR products or digested genomic DNA. The polymorphism may also be detected by restriction fragment length polymorphism (RFLP) analysis, the single-stranded conformation polymorphism of the PCR product (SSCP-PCR), PCR amplification of specific alleles, the amplification of DNA target by PCR followed by single base extension which will be detected by fluorescent or radioactive substances or mass spectrometry, allelic discrimination during PCR, Genetic Bit Analysis, Pyrosequencing, oligonucleotide ligation assay, analysis of melting curves or other methods which detect differences in the length of a DNA fragment at this region or detect a single nucleotide substitution.

Another embodiment of the invention includes novel PCR primers comprising 4 to 30 contiguous bases on either side of the polymorphism to provide an amplification system allowing for detection of the polymorphism by PCR and identification of the fragments by standard methods. Any primers amplifying the region of the polymorphism may be used as taught herein and are also publically available.

The preferred primers for revealing the 12 bp deletion are PSEQDF: 5'-GGA GAT CAT CGG CAG CAT CAA G-3' (SEQ ID NO:8), wherein the 5' end is at position 3786 of the mouse IGF-1R gene and PSEQDR: 5'-GCC ATT CTC AGC CTT GTG TCC-3' (SEQ ID NO:9), wherein the 5' end is at the position 4002 of the mouse IGF-1R gene.

The preferred primers for revealing the A to G substitution in exon 21 of the IGF-1R gene are PSECAF: 5'-GCA TGT GCT GGC AGT ATA ACC-3' (SEQ ID NO:10), wherein the 5' end is at position 3743 of the IGF-1R gene and PSECAR: 5'CAG AGG CCC ATG TCA GTT AAG (SEQ ID NO:11), wherein the 5' end is at position 4376 of the IGF-1R gene.

The preferred primers for revealing the G to A substitution in intron 16 of the IGF-1R gene are PSEQ16F: 5' AGA GTG GCC ATC AAG ACG GTA 3' (SEQ ID NO:12) and PSEQ16R: 5' GGC CTC AGA GAC CGG AGA T 3' (SEQ ID NO:13).

In porcine, the preferred primers for revealing SNP16i27 identified with an *AvaII* restriction site are Primer 16: 5' – CCT CCG TGA TGA AGG AGT TC – 3' (SEQ ID NO:14) and Primer 17: 5' – TCA GTT CCA TGA TGA CCA GC – 3' (SEQ ID NO:15).

The preferred primers for revealing SNP16i73 identified with a *MnlI* restriction site are Primer 16: 5' – CCT CCG TGA TGA AGG AGT TC – 3' (SEQ ID NO:16) and Primer 17: 5' – TCA GTT CCA TGA TGA CCA GC – 3' (SEQ ID NO:17).

The preferred primers for revealing SNP1772 identified with a *TaqI* restriction site are designated as Primer 9: 5' – GGA GTA TGA TGG GCA GGA T – 3' (SEQ ID NO:18) and Primer 8: 5' – GAA GCA TTG GTG CGA ATG TA – 3' (SEQ ID NO:19). Computer programs available on the world wide web allows one of ordinary skill in the art to design other primers capable of amplifying polymorphic segments of the IGF-1R gene such as those shown above and depicted in Table 1. See Steve Rozen and Helen J. Skaletsky (2000) Primer3 on the WWW for general users and for biologist programmers. In: Krawetz S, Misener S (eds) *Bioinformatics Methods and Protocols: Methods in Molecular Biology.* Humana Press, Totowa, NJ, pp 365-386.

A further embodiment comprises a breeding method whereby assays of the above types are conducted on a plurality of gene sequences from different animals or animal embryos of various species to be selected from and, based on the results, certain animals are either selected or dropped out of the breeding program.

The following is a general overview of techniques which can be used to assay for the polymorphisms of the invention.

In the present invention, a sample of genetic material is obtained from an animal. Samples can be obtained from blood, tissue, semen, etc. Generally, peripheral blood cells are used as the source, and the genetic material is DNA. A sufficient amount of cells are obtained to provide a sufficient amount of DNA for analysis. This amount will be known or readily determinable by those skilled in the art. The DNA is isolated from the blood cells by techniques known to those skilled in the art.

Isolation and Amplification of Nucleic Acid

Samples of genomic DNA are isolated from any convenient source including saliva, buccal cells, hair roots, blood, cord blood, amniotic fluid, interstitial fluid, peritoneal fluid, chorionic villus, and any other suitable cell or tissue sample with intact nuclei. The cells can also be obtained from solid tissue as from a fresh or preserved organ or from a tissue sample or biopsy. The sample can contain compounds which are not naturally intermixed with the biological material such as preservatives, anticoagulants, buffers, fixatives, nutrients, antibiotics, or the like.

Methods for isolation of genomic DNA from these various sources are described in, for example, Kirby, *DNA Fingerprinting, An Introduction*, W.H. Freeman & Co. New York (1992). Genomic DNA can also be isolated from cultured primary or secondary cell cultures or from transformed cell lines derived from any of the aforementioned tissue samples.

Samples of animal RNA can also be used. RNA can be isolated from tissues expressing the IGF-1R gene as described in Sambrook et al., supra. RNA can be total cellular RNA, mRNA, poly A+ RNA, or any combination thereof. For best results, the RNA is purified, but can also be unpurified cytoplasmic RNA. RNA can be reverse transcribed to form DNA which is then used as the amplification template, such that the PCR indirectly amplifies a specific population of RNA transcripts. See, e.g., Sambrook, supra, Kawasaki et al., Chapter 8 in *PCR Technology*, (1992) *supra*, and Berg et al., Hum. Genet. 85:655-658 (1990).

PCR Amplification

The most common means for amplification is polymerase chain reaction (PCR), as described in U.S. Pat. Nos. 4,683,195, 4,683,202, 4,965,188 each of which is hereby incorporated by reference. If PCR is used to amplify the target regions in blood cells, heparinized whole blood should be drawn in a sealed vacuum tube kept separated from other samples and handled with clean gloves. For best results, blood should be processed immediately after collection; if this is impossible, it should be kept in a sealed container at 4°C until use. Cells in other physiological fluids may also be assayed. When using any of these fluids, the cells in the fluid should be separated from the fluid component by centrifugation.

Tissues should be roughly minced using a sterile, disposable scalpel and a sterile needle (or two scalpels) in a 5 mm Petri dish. Procedures for removing paraffin from tissue sections are described in a variety of specialized handbooks well known to those skilled in the art.

To amplify a target nucleic acid sequence in a sample by PCR, the sequence must be accessible to the components of the amplification system. One method of isolating target DNA is crude extraction which is useful for relatively large samples. Briefly,

mononuclear cells from samples of blood, amniocytes from amniotic fluid, cultured chorionic villus cells, or the like are isolated by layering on sterile Ficoll-Hypaque gradient by standard procedures. Interphase cells are collected and washed three times in sterile phosphate buffered saline before DNA extraction. If testing DNA from peripheral blood lymphocytes, an osmotic shock (treatment of the pellet for 10 sec with distilled water) is suggested, followed by two additional washings if residual red blood cells are visible following the initial washes. This will prevent the inhibitory effect of the heme group carried by hemoglobin on the PCR reaction. If PCR testing is not performed immediately after sample collection, aliquots of 10^6 cells can be pelleted in sterile Eppendorf tubes and the dry pellet frozen at -20°C until use.

The cells are resuspended (10^6 nucleated cells per 100 µl) in a buffer of 50 mM Tris-HCl (pH 8.3), 50 mM KCl 1.5 mM $MgCl_2$, 0.5% Tween 20, 0.5% NP40 supplemented with 100 µg/ml of proteinase K. After incubating at 56°C for 2 hr. the cells are heated to 95°C for 10 min to inactivate the proteinase K and immediately moved to wet ice (snap-cool). If gross aggregates are present, another cycle of digestion in the same buffer should be undertaken. Ten µl of this extract is used for amplification.

When extracting DNA from tissues, e.g., chorionic villus cells or confluent cultured cells, the amount of the above mentioned buffer with proteinase K may vary according to the size of the tissue sample. The extract is incubated for 4-10 hrs at 50°-60°C and then at 95°C for 10 minutes to inactivate the proteinase. During longer incubations, fresh proteinase K should be added after about 4 hr at the original concentration.

When the sample contains a small number of cells, extraction may be accomplished by methods as described in Higuchi, "Simple and Rapid Preparation of Samples for PCR", in *PCR Technology*, Ehrlich, H.A. (ed.), Stockton Press, New York, which is incorporated herein by reference. PCR can be employed to amplify target regions in very small numbers of cells (1000-5000) derived from individual colonies from bone marrow and peripheral blood cultures. The cells in the sample are suspended in 20 µl of PCR lysis buffer (10 mM Tris-HCl (pH 8.3), 50 mM KCl, 2.5 mM $MgCl_2$, 0.1 mg/ml gelatin, 0.45% NP40, 0.45% Tween 20) and frozen until use. When PCR is to be performed, 0.6 µl of proteinase K (2 mg/ml) is added to the cells in the PCR lysis buffer. The sample is then heated to about

60°C and incubated for 1 hr. Digestion is stopped through inactivation of the proteinase K by heating the samples to 95°C for 10 min and then cooling on ice.

A relatively easy procedure for extracting DNA for PCR is a salting out procedure adapted from the method described by Miller et al., *Nucleic Acids Res.* 16:1215 (1988), which is incorporated herein by reference. Mononuclear cells are separated on a Ficoll-Hypaque gradient. The cells are resuspended in 3 ml of lysis buffer (10 mM Tris-HCl, 400 mM NaCl, 2 mM Na_2 EDTA, pH 8.2). Fifty µl of a 20 mg/ml solution of proteinase K and 150 µl of a 20% SDS solution are added to the cells and then incubated at 37°C overnight. Rocking the tubes during incubation will improve the digestion of the sample. If the proteinase K digestion is incomplete after overnight incubation (fragments are still visible), an additional 50 µl of the 20 mg/ml proteinase K solution is mixed in the solution and incubated for another night at 37°C on a gently rocking or rotating platform. Following adequate digestion, one ml of a 6M NaCl solution is added to the sample and vigorously mixed. The resulting solution is centrifuged for 15 minutes at 3000 rpm. The pellet contains the precipitated cellular proteins, while the supernatant contains the DNA. The supernatant is removed to a 15 ml tube that contains 4 ml of isopropanol. The contents of the tube are mixed gently until the water and the alcohol phases have mixed and a white DNA precipitate has formed. The DNA precipitate is removed and dipped in a solution of 70% ethanol and gently mixed. The DNA precipitate is removed from the ethanol and air-dried. The precipitate is placed in distilled water and dissolved.

Kits for the extraction of high-molecular weight DNA for PCR include a Genomic Isolation Kit A.S.A.P. (Boehringer Mannheim, Indianapolis, Ind.), Genomic DNA Isolation System (GIBCO BRL, Gaithersburg, Md.), Elu-Quik DNA Purification Kit (Schleicher & Schuell, Keene, N.H.), DNA Extraction Kit (Stratagene, LaJolla, Calif.), TurboGen Isolation Kit (Invitrogen, San Diego, Calif.), and the like. Use of these kits according to the manufacturer's instructions is generally acceptable for purification of DNA prior to practicing the methods of the present invention.

The concentration and purity of the extracted DNA can be determined by spectrophotometric analysis of the absorbance of a diluted aliquot at 260 nm and 280 nm. After extraction of the DNA, PCR amplification may proceed. The first step of each cycle of the PCR involves the separation of the nucleic acid duplex formed by the primer

extension. Once the strands are separated, the next step in PCR involves hybridizing the separated strands with primers that flank the target sequence. The primers are then extended to form complementary copies of the target strands. For successful PCR amplification, the primers are designed so that the position at which each primer hybridizes along a duplex sequence is such that an extension product synthesized from one primer, when separated from the template (complement), serves as a template for the extension of the other primer. The cycle of denaturation, hybridization, and extension is repeated as many times as necessary to obtain the desired amount of amplified nucleic acid.

In a particularly useful embodiment of PCR amplification, strand separation is achieved by heating the reaction to a sufficiently high temperature for a sufficient time to cause the denaturation of the duplex but not to cause an irreversible denaturation of the polymerase (see U.S. Pat. No. 4,965,188, incorporated herein by reference). Typical heat denaturation involves temperatures ranging from about 80°C to 105°C for times ranging from seconds to minutes. Strand separation, however, can be accomplished by any suitable denaturing method including physical, chemical, or enzymatic means. Strand separation may be induced by a helicase, for example, or an enzyme capable of exhibiting helicase activity. For example, the enzyme RecA has helicase activity in the presence of ATP. The reaction conditions suitable for strand separation by helicases are known in the art (see Kuhn Hoffman-Berling, 1978, *CSH-Quantitative Biology*, 43:63-67; and Radding, 1982, *Ann. Rev. Genetics* 16:405-436, each of which is incorporated herein by reference).

Template-dependent extension of primers in PCR is catalyzed by a polymerizing agent in the presence of adequate amounts of four deoxyribonucleotide triphosphates (typically dATP, dGTP, dCTP, and dTTP) in a reaction medium comprised of the appropriate salts, metal cations, and pH buffering systems. Suitable polymerizing agents are enzymes known to catalyze template-dependent DNA synthesis. In some cases, the target regions may encode at least a portion of a protein expressed by the cell. In this instance, mRNA may be used for amplification of the target region. Alternatively, PCR can be used to generate a cDNA library from RNA for further amplification, the initial template for primer extension is RNA. Polymerizing agents suitable for synthesizing a complementary, copy-DNA (cDNA) sequence from the RNA template are reverse transcriptase (RT), such as avian myeloblastosis virus RT, Moloney murine leukemia virus

RT, or Thermus thermophilus (Tth) DNA polymerase, a thermostable DNA polymerase with reverse transcriptase activity marketed by Perkin Elmer Cetus, Inc. Typically, the genomic RNA template is heat degraded during the first denaturation step after the initial reverse transcription step leaving only DNA template. Suitable polymerases for use with a DNA template include, for example, *E. coli* DNA polymerase I or its Klenow fragment, T4 DNA polymerase, Tth polymerase, and *Taq* polymerase, a heat-stable DNA polymerase isolated from *Thermus aquaticus* and commercially available from Perkin Elmer Cetus, Inc. The latter enzyme is widely used in the amplification and sequencing of nucleic acids. The reaction conditions for using *Taq* polymerase are known in the art and are described in Gelfand, 1989, PCR Technology, *supra*.

Allele Specific PCR

Allele-specific PCR differentiates between target regions differing in the presence of a polymorphism. PCR amplification primers are chosen which bind only to certain alleles of the target sequence. This method is described by Gibbs, *Nucleic Acid Res.* 17:12427-2448 (1989).

Allele Specific Oligonucleotide Screening Methods

Further diagnostic screening methods employ the allele-specific oligonucleotide (ASO) screening methods, as described by Saiki et al., *Nature* 324:163-166 (1986). Oligonucleotides with one or more base pair mismatches are generated for any particular allele. ASO screening methods detect mismatches between variant target genomic or PCR amplified DNA and non-mutant oligonucleotides, showing decreased binding of the oligonucleotide relative to a mutant oligonucleotide. Oligonucleotide probes can be designed that under low stringency will bind to both polymorphic forms of the allele, but which at high stringency, bind to the allele to which they correspond. Alternatively, stringency conditions can be devised in which an essentially binary response is obtained, i.e., an ASO corresponding to a variant form of the target gene will hybridize to that allele, and not to the wild-type allele.

Ligase Mediated Allele Detection Method

Target regions of the DNA of a test subject can be compared with target regions in unaffected and affected family members by ligase-mediated allele detection. See Landegren et al., Science 241:107-1080 (1988). Ligase may also be used to detect point mutations in the ligation amplification reaction described in Wu et al., *Genomics* 4:560-569 (1989). The ligation amplification reaction (LAR) utilizes amplification of specific DNA sequence using sequential rounds of template dependent ligation as described in Wu, *supra*, and Barany, *Proc. Nat. Acad. Sci.* 88:189-193 (1990).

Denaturing Gradient Gel Electrophoresis

Amplification products generated using the polymerase chain reaction can be analyzed by the use of denaturing gradient gel electrophoresis. Different alleles can be identified based on the different sequence-dependent melting properties and electrophoretic migration of DNA in solution. DNA molecules melt in segments, termed melting domains, under conditions of increased temperature or denaturation. Each melting domain melts cooperatively at a distinct, base-specific melting temperature (T_m). Melting domains are at least 20 base pairs in length, and may be up to several hundred base pairs in length.

Differentiation between alleles based on sequence specific melting domain differences can be assessed using polyacrylamide gel electrophoresis, as described in Chapter 7 of Erlich, ed., *PCR Technology*, Principles and Applications for DNA Amplification, W.H. Freeman and Co., New York (1992), the contents of which are hereby incorporated by reference.

Generally, a target region to be analyzed by denaturing gradient gel electrophoresis is amplified using PCR primers flanking the target region. The amplified PCR product is applied to a polyacrylamide gel with a linear denaturing gradient as described in Myers et al., *Meth. Enzymol.* 155:501-527 (1986), and Myers et al., in *Genomic Analysis, A Practical Approach*, K. Davies Ed. IRL Press Limited, Oxford, pp. 95-139 (1988), the contents of which are hereby incorporated by reference. The electrophoresis system is maintained at a temperature slightly below the Tm of the melting domains of the target sequences.

In an alternative method of denaturing gradient gel electrophoresis, the target sequences may be initially attached to a stretch of GC nucleotides, termed a GC clamp, as described in Chapter 7 of Erlich, *supra*. Preferably, at least 80% of the nucleotides in the GC clamp are either guanine or cytosine. Preferably, the GC clamp is at least 30 bases long. This method is particularly suited to target sequences with high T_m's.

Generally, the target region is amplified by the polymerase chain reaction as described above. One of the oligonucleotide PCR primers carries at its 5' end, the GC clamp region, at least 30 bases of the GC rich sequence, which is incorporated into the 5' end of the target region during amplification. The resulting amplified target region is run on an electrophoresis gel under denaturing gradient conditions as described above. DNA fragments differing by a single base change will migrate through the gel to different positions, which may be visualized by ethidium bromide staining.

Temperature Gradient Gel Electrophoresis

Temperature gradient gel electrophoresis (TGGE) is based on the same underlying principles as denaturing gradient gel electrophoresis, except the denaturing gradient is produced by differences in temperature instead of differences in the concentration of a chemical denaturant. Standard TGGE utilizes an electrophoresis apparatus with a temperature gradient running along the electrophoresis path. As samples migrate through a gel with a uniform concentration of a chemical denaturant, they encounter increasing temperatures. An alternative method of TGGE, temporal temperature gradient gel electrophoresis (TTGE or tTGGE) uses a steadily increasing temperature of the entire electrophoresis gel to achieve the same result. As the samples migrate through the gel the temperature of the entire gel increases, leading the samples to encounter increasing temperature as they migrate through the gel. Preparation of samples, including PCR amplification with incorporation of a GC clamp, and visualization of products are the same as for denaturing gradient gel electrophoresis.

Single-Strand Conformation Polymorphism Analysis

Target sequences or alleles at the IGF-1R locus can be differentiated using single-strand conformation polymorphism analysis, which identifies base differences by alteration in electrophoretic migration of single stranded PCR products, as described in Orita et al., *Proc. Nat. Acad. Sci.* 85:2766-2770 (1989). Amplified PCR products can be generated as described above, and heated or otherwise denatured, to form single stranded amplification products. Single-stranded nucleic acids may refold or form secondary structures which are partially dependent on the base sequence. Thus, electrophoretic mobility of single-stranded amplification products can detect base-sequence difference between alleles or target sequences.

Chemical or Enzymatic Cleavage of Mismatches

Differences between target sequences can also be detected by differential chemical cleavage of mismatched base pairs, as described in Grompe et al., *Am. J. Hum. Genet.* 48:212-222 (1991). In another method, differences between target sequences can be detected by enzymatic cleavage of mismatched base pairs, as described in Nelson et al., *Nature Genetics* 4:11-18 (1993). Briefly, genetic material from an animal and an affected family member may be used to generate mismatch free heterohybrid DNA duplexes. As used herein, "heterohybrid" means a DNA duplex strand comprising one strand of DNA from one animal, and a second DNA strand from another animal, usually an animal differing in the phenotype for the trait of interest. Positive selection for heterohybrids free of mismatches allows determination of small insertions, deletions or other polymorphisms that may be associated with IGF-1R polymorphisms.

Non-gel Systems

Other possible techniques include non-gel systems such as TAQMAN™ (Perkin Elmer). In this system oligonucleotide PCR primers are designed that flank the mutation in question and allow PCR amplification of the region. A third oligonucleotide probe is then designed to hybridize to the region containing the base subject to change between different alleles of the gene. This probe is labeled with fluorescent dyes at both the 5' and 3' ends. These dyes are chosen such that while in this proximity to each other the fluorescence of

one of them is quenched by the other and cannot be detected. Extension by *Taq* DNA polymerase from the PCR primer positioned 5' on the template relative to the probe leads to the cleavage of the dye attached to the 5' end of the annealed probe through the 5' nuclease activity of the *Taq* DNA polymerase. This removes the quenching effect allowing detection of the fluorescence from the dye at the 3' end of the probe. The discrimination between different DNA sequences arises through the fact that if the hybridization of the probe to the template molecule is not complete, i.e., there is a mismatch of some form, the cleavage of the dye does not take place. Thus only if the nucleotide sequence of the oligonucleotide probe is completely complimentary to the template molecule to which it is bound will quenching be removed. A reaction mix can contain two different probe sequences each designed against different alleles that might be present thus allowing the detection of both alleles in one reaction.

Yet another technique includes an Invader Assay which includes isothermic amplification that relies on a catalytic release of fluorescence.

Non-PCR Based DNA Diagnostics

The identification of a DNA sequence linked to IGF-1R can be made without an amplification step, based on polymorphisms including restriction fragment length polymorphisms in an animal and a family member. Hybridization probes are generally oligonucleotides which bind through complementary base pairing to all or part of a target nucleic acid. Probes typically bind target sequences lacking complete complementarity with the probe sequence depending on the stringency of the hybridization conditions. The probes are preferably labeled directly or indirectly, such that by assaying for the presence or absence of the probe, one can detect the presence or absence of the target sequence. Direct labeling methods include radioisotope labeling, such as with ^{32}P or ^{35}S. Indirect labeling methods include fluorescent tags, biotin complexes which may be bound to avidin or streptavidin, or peptide or protein tags. Visual detection methods include photoluminescents, Texas red, rhodamine and its derivatives, red leuco dye and 3,3',5,5'-tetramethylbenzidine (TMB), fluorescein, and its derivatives, dansyl, umbelliferone and the like or with horse radish peroxidase, alkaline phosphatase and the like.

Hybridization probes include any nucleotide sequence capable of hybridizing to the mouse chromosome where IGF-1R resides, and thus defining a genetic marker linked to IGF-1R, including a restriction fragment length polymorphism, a hypervariable region, repetitive element, or a variable number tandem repeat. Hybridization probes can be any gene or a suitable analog. Further suitable hybridization probes include exon fragments or portions of cDNAs or genes known to map to the relevant region of the chromosome.

Preferred tandem repeat hybridization probes for use according to the present invention are those that recognize a small number of fragments at a specific locus at high stringency hybridization conditions, or that recognize a larger number of fragments at that locus when the stringency conditions are lowered.

One or more additional restriction enzymes and/or probes and/or primers can be used. Additional enzymes, constructed probes, and primers can be determined by routine experimentation by those of ordinary skill in the art and are intended to be within the scope of the invention.

Although the methods described herein may be in terms of the use of a single restriction enzyme and a single set of primers, the methods are not so limited. One or more additional restriction enzymes and/or probes and/or primers can be used, if desired. Indeed in some situations it may be preferable to use combinations of markers giving specific haplotypes. Additional enzymes, constructed probes and primers can be determined through routine experimentation, combined with the teachings provided and incorporated herein. Stand alone software as well as web-based software are avaible that allows the user to identify other restriction mapping sites in the DNA sequence, e.g., http://www.restrictionmapper.org/.

According to the invention, polymorphisms in the IGF-1R gene have been identified which have been associated with reproductive longevity and/or sustained performance under stress. The presence or absence of the markers, in one embodiment may be assayed by PCR-RFLP analysis using the restriction endonucleases and amplification primers may be designed using analogous human, mouse, or other IGF-1R sequences due to high homology in the region surrounding the polymorphisms, or may be designed using known IGF-1R gene sequence data as exemplified in Genbank or even designed from sequences obtained from linkage data from closely surrounding genes based

upon the teachings and references herein. The sequences surrounding the polymorphism will facilitate the development of alternate PCR tests in which a primer of about 4-30 contiguous bases taken from the sequence immediately adjacent to the polymorphism is used in connection with a polymerase chain reaction to greatly amplify the region before treatment with the desired restriction enzyme. The primers need not be the exact complement; substantially equivalent sequences are acceptable. The design of primers for amplification by PCR is known to those of skill in the art and is discussed in detail in Ausubel (ed.), "Short Protocols in Molecular Biology, Fourth Edition" John Wiley and Sons 1999. The following is a brief description of primer design.

Primer Design Strategy

Increased use of polymerase chain reaction (PCR) methods has stimulated the development of many programs to aid in the design or selection of oligonucleotides used as primers for PCR. Four examples of such programs that are freely available via the Internet are: PRIMER by Mark Daly and Steve Lincoln of the Whitehead Institute (UNIX, VMS, DOS, and Macintosh), Oligonucleotide Selection Program (OSP) by Phil Green and LaDeana Hiller of Washington University in St. Louis (UNIX, VMS, DOS, and Macintosh), PGEN by Yoshi (DOS only), and Amplify by Bill Engels of the University of Wisconsin (Macintosh only). Generally these programs help in the design of PCR primers by searching for bits of known repeated-sequence elements and then optimizing the T_m by analyzing the length and GC content of a putative primer. Commercial software is also available and primer selection procedures are rapidly being included in most general sequence analysis packages.

Sequencing and PCR Primers

Designing oligonucleotides for use as either sequencing or PCR primers requires selection of an appropriate sequence that specifically recognizes the target, and then testing the sequence to eliminate the possibility that the oligonucleotide will have a stable secondary structure. Inverted repeats in the sequence can be identified using a repeat-identification or RNA-folding program such as those described above (see prediction of Nucleic Acid Structure). If a possible stem structure is observed, the sequence of the

primer can be shifted a few nucleotides in either direction to minimize the predicted secondary structure. The sequence of the oligonucleotide should also be compared with the sequences of both strands of the appropriate vector and insert DNA. Obviously, a sequencing primer should only have a single match to the target DNA. It is also advisable to exclude primers that have only a single mismatch with an undesired target DNA sequence. For PCR primers used to amplify genomic DNA, the primer sequence should be compared to the sequences in the GenBank database to determine if any significant matches occur. If the oligonucleotide sequence is present in any known DNA sequence or, more importantly, in any known repetitive elements, the primer sequence should be changed. Depending on the desired test conditions, the sequences of the primers should be designed to provide for both efficient and faithful replication of the target nucleic acid. Methods of PCR primer design are common and well known in the art. (Rychlik, W. (1993) In White, B. A. (ed.), Methods in Molecular Biology, Vol. 15, pages 31-39, *PCR Protocols: Current Methods and Applications*. Humania Press, Inc., Totowa, N.J.).

The methods and materials of the invention may be used as the basis to search for polymorphisms in the IGF-1R gene of species that are associated with reproductive longevity and sustained performance under stress. This would allow uses to genetically type individual animals by detecting genetic differences in those animals. For instance, a sample of mouse genomic DNA may be evaluated by reference to one or more controls to determine if a polymorphism in the IGF-1R gene is present. Preferably, RFLP analysis is performed with respect to the mouse IGF-1R gene, and the results are compared with a control. The control is the result of a RFLP analysis of the mouse IGF-1R gene of a different mouse where the polymorphism of the mouse IGF-1R gene is known. Similarly, the IGF-1R genotype of a mouse may be determined by obtaining a sample of its genomic DNA, conducting RFLP analysis of the IGF-1R gene in the DNA, and comparing the results with a control. Again, the control is the result of RFLP analysis of the IGF-1R gene of a different mouse. The results genetically type the mouse by specifying the polymorphism(s) in its IGF-1R genes. Finally, genetic differences among mice can be detected by obtaining samples of the genomic DNA from at least two mice, identifying the presence a polymorphism in the IGF-1R gene, and comparing the results.

Such assays are useful for identifying the genetic markers relating reproductive longevity and the ability to sustained stress factors such as lactation and pregnancy, as discussed above and for the general scientific analysis of mouse genotypes' and phenotypes'.

The examples and methods herein disclose certain genes which have been identified to have a polymorphism which is associated either positively or negatively with a beneficial trait that will have an effect on performance under stress in animals, such as cattle, birds, and aquatic species, such as shrimp carrying this polymorphism. The identification of the existence of a polymorphism within a gene is often made by a single base alternative that results in a restriction site in certain allelic forms. A certain allele, however, as demonstrated and discussed herein, may have a number of base changes associated with it that could be assayed for which are indicative of the same polymorphism (allele). Further, other genetic markers or genes may be linked to the polymorphisms disclosed herein so that assays may involve identification of other genes or gene fragments, but which ultimately rely upon genetic characterization of animals for the same polymorphism. Any assay which sorts and identifies animals based upon the allelic differences disclosed herein are intended to be included within the scope of this invention.

Linkage Analysis

Diagnostic screening may be performed for polymorphisms that are genetically linked to a phenotypic variant in IGF-1R activity or expression, particularly through the use of microsatellite markers or single nucleotide polymorphisms (SNP). The microsatellite or SNP polymorphism itself may not be phenotypically expressed, but is linked to sequences that result in altered activity or expression. Two polymorphic variants may be in linkage disequilibrium, i.e., where alleles show non-random associations between genes even though individual loci are in Hardy-Weinberg equilibrium.

Linkage analysis may be performed alone, or in combination with direct detection of phenotypically evident polymorphisms. The use of microsatellite markers for genotyping is well documented. For examples, see Mansfield et al. (1994) *Genomics* 24:225-233; and Ziegle et al. (1992) *Genomics* 14:1026-1031. The use of SNPs for genotyping is illustrated in Underhill et al. (1996) *Proc. Natl. Acad. Sci. USA* 93:196-200.

Genetic linkage maps show the relative locations of specific DNA markers along a chromosome. Any inherited physical or molecular characteristic that differs among animals and is easily detectable in the laboratory is a potential genetic marker. DNA sequence polymorphisms are useful markers because they are plentiful and easy to characterize precisely. Many such polymorphisms are located in non-coding regions and do not affect the phenotype of the organism, yet they are detectable at the DNA level and can be used as markers. Examples include restriction fragment length polymorphisms (RFLPs), which reflect sequence variations in DNA sites or differences in the length of the product, which can be cleaved by DNA restriction enzymes, microsatellite markers, which are short repeated sequences that vary in the number of repeated units, single nucleotide polymorphisms (SNPs), and the like.

The "linkage" aspect of the map is a measure of how frequently two markers are inherited together. The closer the markers are to each other physically, the less likely a recombination event will fall between and separate them. Recombination frequency thus provides an estimate of the distance between two markers. The value of the genetic map is that an inherited trait can be located on the map by following the inheritance of a DNA marker present in affected animals, but absent in unaffected animals, even though the molecular basis for the trait may not yet be understood.

SNPs are generally biallelic systems, that is, there are two alleles that a population may have for any particular marker. This means that the information content per SNP marker is relatively low when compared to microsatellite markers, which may have upwards of 10 alleles. SNPs also tend to be population-specific; a marker that is polymorphic in one population may not be very polymorphic in another. SNP markers offer a number of benefits that will make them an increasingly valuable tool. SNPs, found approximately every kilobase (see Wang et al. (1998) *Science* 280:1077-1082), offer the potential for generating high density genetic maps, which will be extremely useful for developing haplotyping systems for genes or regions of interest, and because of the nature of SNPs, they may in fact be the polymorphisms associated with the traits under study. The low mutation rate of SNPs also makes them excellent markers for studying complex genetic traits.

One of skill in the art, once a polymorphism has been identified and a correlation to a particular trait established, will understand that there are many ways to genotype animals for this polymorphism. The design of such alternative tests merely represents optimization of parameters known to those of skill in the art and is intended to be within the scope of this invention as fully described herein.

The following examples serves to better illustrate the invention described herein and are not intended to limit the invention in any way. Those skilled in the art will recognize that there are several different parameters which may be altered using routine experimentation and which are intended to be within the scope of this invention.

Example 1

Identify polymorphisms at the *daf-2* (Insulin-like growth factor-1 receptor) gene in lines of mice selected for reproductive longevity and evaluating this gene as putative candidates for DNA markers for reproductive longevity in livestock.

Materials and Methods

The mouse population: The original mouse population, which was established by Agriculture and Agri-Food Canada in Ottawa in 1965, was a cross between two strains of mice (P and Q). The P strain was a cross between three inbred lines (C3H/HeJ, C57BL/6J, CBA/J, SWR/J) and the Q was Falconer's strain, which had a substantial heterogeneous background (Garnett and Falconer 1975). Ancestry of the Q strain goes back to 1948, with a large contribution from the 'J' stain (Falconer 1973). The 'J' strain was a heterogeneous population of mixed origin, which was made from crosses between Bateman's high-lactation line, Goodale's and MacArthur's large body weight selected lines, and four mutant stocks with the C57-BL inbred line as part of their ancestry (Brown and Falconer 1960). This population 'was about as close as one could get with laboratory mice to a natural random-bred population' (Brown and Falconer 1960). Several strains were derived from the J stock, including Falconer's control line (JC), an inbred line (JU), and a high litter size selected line (JH). The JC and JU lines constituted half of the ancestry of the Q strain. The other half was from crosses between Goodale's and MacArthur's large body weight selected lines (that had contributed to the J stock), MacArthur's small body weight selected line, JH, and a line that derived from the J stock and had been selected for high growth rate on a restricted diet (Falconer 1960). The four inbred lines and two of the lines that contributed to the Q strain (MacArthur's small body weight selected line (SM/J) and

Goodale's large body weight selected line (LG/J)),are currently maintained at the Jackson Laboratories, Bar Harbor, Maine. The contribution of so many strains to this colony, which is the only non-inbred mouse model in the world selected for reproductive longevity, was important for ensuring that the base population was heterozygous at many loci.

Prior to the implementation of the selection program for reproductive longevity, both the P and Q stocks were maintained by random mating for 23 generations (80 breeding pairs in P and 45 males and 90 females in Q) to achieve linkage equilibrium. Two lines from each of the P and Q strains were then established, each with 92 pairs of breeders. One line derived from each of the P and Q stocks was selected for nursing ability of the mother, and the other for body weight of progeny at 42 days of age. After 21 generations of selection, these four lines were crossed, and the synthetic stock was maintained by random mating for 12 generations to allow it to approach linkage equilibrium. One control (C1) and two selected lines, with (SA1) and without (SU1) standardizing litter size to 8, were established in 1982 and have been continuously selected for reproductive longevity since then (Nagai *et al.* 1995). Replications from each of the control and selected lines were established (C2, SA2, SU2) in 1993 using the existing lines (generation 18 of the SA1 and SU1 and generation 44 of the C1). Also, the high performing animals from the different selected lines were mated to generate a new line with a more diverse genetic background, and a sample from the control lines was used to generate a new control line. In each of the selected lines, one male and one female were caged at about eight weeks of age, and each pair was maintained in the same cage continuously until the next generation was established, using progeny from the latest parities. In the control lines, progenies from the first parity were used as breeders. The control and selected lines were maintained with 42 and 30 breeding pairs, respectively, avoiding full-sib mating (Nagai *et al.* 1995). Performance of the three original lines (SA1, SA2, C1) at generations 12 and 16 is reported by Nagai *et al.* (1995), and at generation 24 by Farid *et al.* (2002). The average number of days from mating to the last parturition in generation 12 was 236, 265 and 159 for lines SA1, SU1 and C1, respectively, showing that reproductive longevity was improved by 48% in the SA1 and 67% in the SU1. The corresponding values at generation 16 were 79% and 80%, and at generation 24 were 86% and 61% for the SA1 and SU1 lines, respectively. The number of parturitions during lifetime has not changed in the control line (5.34, 4.90,

5.30 at generations 12, 16 and 24, respectively), while the SA1 line showed a steady improvement: 8.63, 8.84 and 10.6 (61.6%, 80.4% and 100%). The corresponding values for the SU1 line were 79.9%, 93.0% and 83.0%.

Source of DNA: DNA was extracted from blood or tissue of 261 breeder males and females from the lines C1 (generation 69), C2 (generation 70), SA1 and SU1 (generation 24), and from one progeny from each of 153 families from lines C1, C2, SA1, SA2, SU1 and SU2. DNA samples from the four inbred lines that have contributed to the base population (C3H/HeJ, C57BL/6J, CBA/J, SWR/J) were obtained from the Jackson Laboratories, Bar Harbor, Maine.

Laboratory procedures: There are two sequences of the mouse insulin-like growth factor-1 receptor cDNA in Genbank (accession numbers AF056187 (SEQ ID NO:1) and XM_133508 (SEQ ID NO:3)), and sequences of most of this gene's exons and introns included in the clone RP23-378H21 (Genbank accession number AC101879) (SEQ ID NO:6). Several overlapping PCR primers were designed to cover the entire coding region of the IGF-1R gene and its 3' UTR using the Oligo 6.0 primer analysis software (Molecular Biology Insight, cascade, CO, USA). Information on a few of these primers which amplified polymorphic regions is shown in Table 1.

Table 1. Information on the primers used to amplify polymorphic segments of the IGF-1R gene in mice.

SEQ ID NO	Primer name	Sequence (5'-3')	Location	MgCl2 (mM)	Anneal. temp. (°C)	Size, bp
8	PSEQDF	GGAGATCATCGGCAGCATCAAG	Exon 21	2.5	58.0	216or 204
9	PSEQDR	GCCATTCTCAGCCTTGTGTCC	Exon 21			
10	PSECAF	GCATGTGCTGGCAGTATAACC	Exon 21	1.5	58.5	634
11	PSECAR	CAGAGGCCCATGTCAGTTAAG	3' UTR			
12	PSEQ16F	AGAGTGGCCATCAAGACGGTA	Exon 16	2.0	58.5	486
13	PSEQ16R	GGCCTCAGAGACCGGAGAT	Exon 17			

PCR amplifications were performed in 50 µL volumes containing (final concentration) 0.1% Tween 20, 1 x PCR buffer, 1.5-2.0 mM $MgCl_2$, 0.2 mM each dNTP,

400 nM each primer, 2 units of *Taq* polymerase (Roche) and 100 ng template DNA. The thermal cycler was set at 95°C for 2 min followed by 34 cycles at 94°C for 1 min, 55-67°C (depending on the primer) for 1 min, 72°C for 1 min and a final 9 min extension at 72°C. Long fragments were amplified using PCR cocktails similar to those explained above, except using 0.35 mM of each dNTP and 2.5 units of Long-Range *Taq* polymerase (Roche). Thermal cycler was set at an initial 2 min denaturation at 95°C, followed by 10 cycles of 94°C for 10 sec, 55-67°C for 30 sec and 68°C for 10 min. The next 20 cycles consisted of 94°C for 10 sec, annealing at 55-67°C for 30 sec, elongation at 68°C for 10 min plus an additional 20 sec for each new cycle and a final 9 min extension at 68°C.

Genotyping for the12 bp deletion in exon 21 was performed using the GenScan option of an ABI 377 automated DNA sequencer. Two primers flanking the deletion were designed. The Hex Amidite label was placed on the forward primer. Since the deletion was from 3896 to 3907, the PCR product was 216 bp in the wild type (4002-3786) or 204 bp for the deletion. The PCR cocktail contained 1.25 µL of a 10X buffer, 1.25 µL of a 25mM $MgCl_2$, 1.0 µL of a 1.25 mM dNTPs, 5 pmol of each primer, 0.2 µL of a 5 U/µL Amplitaq gold polymerase, 25 ng of DNA and water to 12.5 µL total volume. Thermal cycler conditions were 95°C for 8 minutes initial denaturation, followed by 30 cycles of 95°C for 30 sec, 58°C for 30 sec, 72°C for 60 sec, and a final extension of 72°C for 30 minutes. PCR products were maintained at 6°C until processed. One µL of PCR products were loaded into the sequencer.

Data analysis:

Conformation of genotype frequencies to Hardy-Weinberg equilibrium was tested using the GENEPOP computer package (http://wbiomed.curtin.edu.au/genepop) using the default options (1000 dememorisation, 100 batches and 1000 iterations). The program uses the Markov chain method to estimate the exact Hardy-Weinberg probability without bias (Guo and Thompson, 1992). The probability of rejecting H_o, i.e., genotype frequencies are in Hardy-Weinberg equilibrium and the standard error of this estimate were computed. When standard errors were larger than 0.01, the data were re-analysed using a larger number of batches. This program does not perform any test when a locus is monomorphic or quasi monomorphic (two alleles, but one is represented only once).

Pairwise tests for homogeneity of allele and genotype frequency distributions were also performed using the GENEPOP computer package which follows the Raymond and Rousset (1995) method. The hypotheses tested were that allele and genotype distributions were independent of lines (no difference between lines). An unbiased estimate of the Fisher's exact test on contingency tables is performed using the Markov chain method (1000 dememorisation, 100 batches and 1000 iterations). The program computes the probability of being wrong when H_o is rejected. Rare alleles (frequency of less than 5%) were not pooled together prior to the above tests. F_{IS} statistics, as the measures of inbreeding within each line (Wright, 1943, 1978), were computed for each polymorphic site in every line using the GENEPOP computer program.

Results

Polymorphism: A total of 4434 bp of the IGF-1R gene, consisting of exons 2, 3, 9, 10, 12, 13, 14, 15, 16, 17 and 21 (2344 bp) and introns 10, 12, 13, 14 and 16 (2090 bp) in five to seven individuals from each of the three main lines (C1, SA1, SU1) were sequenced. No polymorphism was detected in exons 2, 3, 9, 10, 12, 13, 14, 15, 16, 17 or in introns 10, 12, 13 and 14. The following polymorphic sites have been detected:

Site A: A 'G' to 'A' substitution (GGTC to GATC) was detected in intron 16 of the gene. The 486 bp PCR product, spanning exons 16 and 17 and intron 16, was cut into 454 and 32 bp fragments (A_1 allele) by the enzyme *DpnII* (↑GATC). This nucleotide substitution resulted in the creation of a new recognition site for this enzyme, which cleaved the 454 bp fragment into 328 and 125 bp fragments (A_2 allele). In addition, sequence information revealed a 'G' nucleotide insertion in intron 16, 153 bp 5' to the above point mutation, but no restriction enzyme was found for discriminatory typing of this insertion.

Site B: An *HpaII* (C↑CGG) polymorphism was detected as a result of an 'A' to 'G' substitution at position 3876 in exon 21 (CCAG to CCGG). The enzyme had one recognition site in the PCR product (373 and 261 bp fragments, B_1 allele) and the nucleotide substitution resulted in an additional recognition site for the enzyme (373, 134 and 127 bp fragments, B_2 allele). This is a silent mutation, as both CCA and CCG code for the amino acid proline. The marker for coping with pregnancy and lactation stress in mice

is the sequence containing the 'A' nucleotide at position 3876 of the mouse IGF-1R gene, identified by the 373/261 bp fragments (B_1 allele). Since the substitution is 20 base pairs upstream from the 12 base pair deletion, the 261 bp and 127 bp bands will shift by 12 base pairs when animals are homozygous or heterozygous for the deletion allele (D_2). As is known in the art, however, restriction patterns are not exact determinants of the sizes of fragments and are only approximate.

Site D: Site D: A 12 bp deletion was detected 20 bp 3' to the site B in exon 21 (positions 3896-3907 of the IGF-1R gene cDNA, Genbank accession number AF056187, SEQ ID NO:1). This 12 bp fragment (tggagatggagc) (SEQ ID NO:20) appears twice in tandem (D_1 allele) in or only once (D_2 allele) in this region, resulting in the deletion of four amino acids (leucine, glutamic acid, methionine, and glutamic acid) from the IGF-1R protein. One IGF-1R sequence (Genbank accession number AF056187, SEQ ID NO:1) has two copies of this fragment while two others (Genbank accession numbers XM_133508 (SEQ ID NO:3) and AC101879 (, SEQ ID NO:6) have one copy.

Allele and genotype frequency distributions: Although sites A and B are approximately 22 kb apart, all 153 juveniles and 261 breeders had exactly the same genotypes at these two sites, constituting only two alleles (A_1 and A_2). Replicate lines of juvenile mice were not different from the main lines for allele or genotype frequencies at site A. The frequency of A_1 allele in breeders from the SU1 line (0.84) was significantly greater than those in the other three lines (0.48, 0.62, 0.63, Tables 2 and 3). A similar pattern was observed in the juveniles, where frequencies of the A_1 allele in the SU1 and SU2 lines (0.83 and 0.89) were significantly greater than those in SA1 (0.55), SA2 (0.46), C1 (0.48) and C2 (0.61) lines (Tables 4 and 5). Frequencies of A_1 allele in the C1 line were similar in breeders and juveniles (0.48), and were smaller than those in the C2 line in breeders (0.67, $P<0.01$) and juveniles (0.61, NS). Frequency of A_1 allele in selected and control lines in which litter size was not standardized (SU1, SU2, C2) was greater than that in the lines in which litter size was standardized (SA1, SA2, C1) in both breeders and juveniles, suggesting that the A_1 allele was possibly selected for under high levels of maternal stress.

The frequency of the A_1A_1 genotype in breeders from SU1 line (0.71) was significantly greater than in other lines, which ranged between 0.23 (C1) and 0.47 (C2)

(Tables 2 and 3). Juveniles from the SU1 and SU2 lines had greater frequencies of the A_1A_1 genotype (0.75 and 0.77) and lower frequencies of the A_2A_2 genotype (0.10 and 0.0) than the other four lines, in which the frequencies of A_1A_1 ranged from 0.17 to 0.44 and frequencies of A_2A_2 ranged from 0.22 to 0.26 (Tables 4 and 5). Differences in genotype frequencies between SU1 and SU2 and the other lines were all significant, except for SU1 and C2 that approached significance (P=0.079). Genotype frequency distributions conformed to Hardy-Weinberg proportions in all the lines. All four inbred lines (C3H/HeJ, C57BL/6J, CBA/J, SWR/J) had the A_1A_1 genotype at site A and the B_1B_1 genotype at site B, indicating that the A_2 and B_2 alleles must have been introduced into the base population by the Q-strain.

No D_2 allele was detected in any of the control mice. The frequency of the D_2 allele (deletion) ranged from 0.10 to 0.19 in the selected lines in the juveniles and breeders. The selected lines within breeder and juvenile groups had comparable allele and genotype frequencies at site D. All selected lines had significantly different allele and genotype frequency distributions compared with the control lines in which the D_1 allele was fixed (Tables 6, 7, 8, 9). Replicate lines of juvenile mice were not different from the main lines for allele or genotype frequencies at site D. Genotype frequency distributions conformed to Hardy-Weinberg proportions in all the lines, except in juveniles from the SA1 line, which was deficient in heterozygotes (F_{IS}=+0.449, Table 4). High proportions of the D_2 allele appeared in the heterozygous state (0.179 to 0.385), and low proportions (0.0 to 0.107) were in homozygous form in all the selected lines, which is expected from a population in Hardy-Weinberg equilibrium in which one allele has a low frequency. The C57BL/6J had the D_2D_2 genotype, but the other three inbred lines had the D_1D_1 genotype.

Only six of the10 possible genotypes were present in the population when the joint distribution of A and D sites was considered (Tables 10, 12), indicating the presence of three of the four possible haplotypes (A_1D_1, A_1D_2, A_2D_1). Haplotype and genotype frequency distributions were significantly different among all the lines within breeder and juvenile groups, except those between replicate lines (Tables 10, 11, 12, 13). Haplotype frequency differences between selected and control lines were largely due to the absence of the A_1D_2 haplotype in the latter. Differences among non-replicate selected lines for haplotype frequency distributions were mainly the result of higher frequencies of A_1D_1

(0.69 to 0.74) and lower frequencies of A_2D_1 (0.12 to 0.18) in selected non-standardized lines compared with those in standardized selected lines, which had lower frequencies of A_1D_1 (0.28 to 0.46) and higher frequencies of A_2D_1 (0.38 to 0.52). Genotype frequencies conformed to Hardy-Weinberg proportions in all the lines in both breeders and juveniles, except in the SA1 line in juveniles, which was deficient in heterozygotes (F_{IS}=+0.341, Table 12). There was no difference between male and female breeders for allele or genotype frequencies at any of the sites (data not shown).

Discussion

Similarities between the replicate lines for allele (haplotype) and genotype frequencies at all sites may indicate that the observed differences among non-replicate lines had happened before divergence of replicate lines from the main lines. These findings also imply that the size of the lines was great enough to make genetic drift a negligible force in changing the genetic profile of the lines in the last 8 generations of the selected lines (generations 18 to 24) and 26 generations of the controls (generations 44 to 69). The observed differences among the lines for allele frequency distributions can thus be largely attributed to the selection pressure applied to each line.

The finding that the A_1 allele had a significantly greater frequency in breeder animals in which litter size was not standardized to 8 (selected and control lines) may suggest that although this gene has not been under selection pressure for reproductive longevity, the A_1 allele may be linked to a QTL that has a favorable effect on maternal stress. Most female mice conceive while still nursing, which imposes a great pressure on them, and the effect will be more pronounced when litter size is large. It seems that the A_1 allele is associated with animals that may be able to better cope with such a stress. This finding has some ramifications in the livestock industry, such as swine and dairy cattle, where lactation and pregnancy often coincide. This is the first evidence showing that such a characteristic is genetically controlled.

The results from site D provide a different picture than of site A. The absence of the D_2 allele (deletion) in the control lines, and the similarity between all the selected lines for the allele and genotype frequencies within breeders and juveniles may suggest that the D_2 allele (or an allele which is linked to D_2) had a negative effect on early reproduction, and

has therefore been eliminated from the control lines. This conclusion is based on three notions. First, the frequency of the D_2 allele in the original population was expected to be at least 0.125, because C57BL/6J with the D_2D_2 genotype provided 1/8 of the genes to the original population, and this line had also contributed to the Q-strain. The effects of 21 generations of selection for nursing ability of the mother and body weight of progeny that was applied to the original population before the establishment of the base population for this experiment is not known. Assuming, however, that the frequency of the D_2 allele was not drastically changed, it is unlikely that the D_2 allele with such a frequency had not been included in the first generation of the control line merely by chance. Second, absence of the D_2 allele in the control lines was not because of the small number of mice that were genotyped. The probability (α) that an allele with the frequency of Y or less in a population falls into a sample of size n (i.e., 2n alleles) is $\log(1-\alpha)=2n \log(1-Y)$. Setting n=25, which was the smallest sample size of the control lines in juveniles, and Y=0.10 (the smallest estimate of the D_2 frequency in any line) will result in α=0.994, i.e., there is at least 99% probability that the D_2 allele with a frequency of 0.10 would be included in a sample of size 25. Combining the two control lines of juveniles will increase this probability to 99.99%. The total number of control mice tested (juveniles and breeders) was 217, suggesting that the D_2 allele certainly does not exist in the control lines. Third, in the control lines, the male is removed from the cage 14 to17 days following pairing. Replacement mice in the control lines are thus selected from females that conceived within the first 14 to 17 days after exposure to a male. The control lines, therefore, have been under mild selection for early reproduction. Although more studies are needed, it seems logical to believe that deletion of four amino acids from the IGF-1R would have some negative effect on the function of this polypeptide. The only explanation for the D_2 allele to have a frequency of 0.10 to 0.20 in the selected lines is that this allele, or one which is linked to it, had a positive effect on reproduction at a later age. In addition, the D_2 allele was largely in the heterozygous state, which will mask any negative effect of the allele.

The D and A sites are only 20 bp apart, and thus the likelihood of a crossing-over between them is very slim. Differences between lines for allele frequencies at sites A and D should be sought in the origin of the haplotypes. Since the only source of the A_2 allele was the Q strain, and there was no A_2D_2 haplotype in the population, it seems logical to assume

that the A_2D_1 haplotype originated from the Q-strain and the A_1D_2 haplotype originated from C57BL/6J (the only inbred line carrying the A_1D_2 haplotype). Line C57BL/6J had a minor contribution to the Q strain, indicating that the Q strain might have carried the A_1D_2 haplotype as well. The A_1D_1 haplotype originated from the other three inbred lines as well as from the Q-strain. It seems reasonable to conclude that the A_1D_2 haplotype, which originated from the C57BL/6J line and has been eliminated from the control lines, is a QTL with a negative effect on early reproduction and a positive effect on reproductive longevity. The A_2D_1 haplotype that originated from the Q strain and had high frequencies in non-standardized lines (SU1, SU2, C2) may be a QTL that has been selected for under maternal pressure (large litter size, high milk production, pregnancy).

F_{IS} is a measure of the inbreeding coefficient of individuals in a subdivided population due to nonrandom mating, or inbreeding of an individual relative to the sub-population to which it belongs (Wright, 1943, 1978; Nei, 1973; Hartl and Clark, 1989). When mating is at random in a sub-population, F_{IS} is equal to zero. Positive F_{IS} values indicate within sub-populations inbreeding (more homozygosity than expected) due to mating between relatives. Negative F_{IS} values show less homozygosity than expected from a population at Hardy-Weinberg equilibrium. Conformation of genotype frequency distributions to Hardy-Weinberg values and small F_{IS} estimates indicate that mating between animals with respect to sites A and D and their joint distribution has been at random in all the lines except SA1 in juveniles. This is expected in view of the fact that the effect of individual alleles on phenotype (reproductive longevity) has not been visible.

Many lines of mice contributed to the base population, making it a heterogeneous stock with many segregating loci upon which selection pressure has been applied for 24 generations. The fact that allele frequencies at sites A and D in the entire sample were 0.63 and 0.89 in juveniles and 0.63 and 0.94 in breeders, respectively, point to the heterogeneity of the population at the present time. The observed genetic variability makes this colony unique.

Table 2. Distribution of allele and genotype frequencies at site A[1] at the IGF-1R locus in breeder mice, test for Hardy-Weinberg equilibrium and F_{IS} estimates by line and sex.

Line	Sex	Allele frequency		Genotype frequency			No. of mice	H-W prob	F_{IS}
		A_1	A_2	A_1A_1	A_2A_2	A_1A_2			
SA1 Selected (standardized)	F	0.648	0.352	0.407	0.111	0.481	27		
	M	0.603	0.397	0.379	0.172	0.448	29		
	Total	0.625	0.375	0.393	0.143	0.464	56	1.00	0.019
SU1 Selected (Non-standardized)	F	0.881	0.119	0.809	0.048	0.143	21		
	M	0.810	0.190	0.619	0.000	0.381	21		
	Total	0.845	0.155	0.714	0.024	0.262	42	1.00	0.011
C1 Control (standardized)	F	0.488	0.512	0.190	0.214	0.595	42		
	M	0.476	0.523	0.262	0.310	0.429	42		
	Total	0.482	0.518	0.226	0.262	0.512	84	1.00	-0.019
C2 Selected (non-standardized)	F	0.700	0.300	0.500	0.100	0.400	40		
	M	0.641	0.359	0.436	0.154	0.410	39		
	Total	0.671	0.329	0.468	0.127	0.405	79	0.45	0.089
Total		0.628	0.372	0.414	0.157	0.429	261	0.99	

1-Site A is a 'G' to 'A' substitution in intron 16, which is in linkage disequilibrium with an 'A' to 'G' substitution in exon 21 (site B).

Table 3. Pairwise comparison of the lines for allele frequency (above diagonal) and genotype frequency (below diagonal) for site A in breeder mice.

Line	SA1	SU1	C1	C2
SA1	-	0.001	0.020	0.436
SU1	0.001	-	0.000	0.003
C1	0.020	0.000	-	0.002

C2	0.446	0.006	0.001	-

Table 4. Distribution of allele and genotype frequencies at site A of the IGF-1R locus in juveniles, test for Hardy-Weinberg equilibrium and F_{IS} estimates by line.

Line		Allele frequency		Genotype frequency			No. of mice	H-W prob.	F_{IS}
		A_1	A_2	A_1A_1	A_2A_2	A_1A_2			
Selected (Standardized)	SA1	0.552	0.448	0.345	0.241	0.414	29	0.45	0.180
	SA2	0.458	0.542	0.167	0.250	0.583	24	0.68	-0.154
Selected (Non-standardized)	SU1	0.825	0.175	0.750	0.100	0.150	20	0.07	0.500
	SU2	0.885	0.115	0.769	0.000	0.231	26	1.00	-0.111
Control (standardized)	C1	0.481	0.519	0.222	0.259	0.519	27	1.00	-0.020
Control (non-standardized)	C2	0.611	0.389	0.444	0.222	0.333	27	0.13	0.316
Total		0.627	0.373	0.438	0.183	0.379	153	0.46	0.109

Table 5. Pairwise comparison of the lines for allele frequency (above diagonal) and genotype frequency (below diagonal) for site A in juveniles.

Line	SA1	SA2	SU1	SU2	C1	C2
SA1	-	0.428	0.005	0.000	0.570	0.567
SA2	0.451	-	0.000	0.000	0.845	0.160
SU1	0.014	0.001	-	0.545	0.001	0.038
SU2	0.000	0.000	0.592	-	0.000	0.001
C1	0.588	0.836	0.002	0.000	-	0.246
C2	0.617	0.189	0.079	0.004	0.279	-

Table 6. Distribution of allele and genotype frequencies of the deletion[1] at the IGF-1R locus in breeder mice, test for Hardy-Weinberg equilibrium and F_{IS} estimates by line and sex.

Line	Sex	Allele frequency		Genotype frequency			H-W Prob	F_{IS}
		D_1	D_2	D_1D_1	D_2D_2	D_1D_2		
SA1 Selected (standardized)	F	0.796	0.204	0.593	0.000	0.407		
	M	0.862	0.138	0.758	0.034	0.207		
	Total	0.830	0.170	0.679	0.018	0.304	1.00	-0.069
SU1 Selected (Non-standardized)	F	0.929	0.071	0.857	0.000	0.143		
	M	0.857	0.143	0.714	0.000	0.286		
	Total	0.893	0.107	0.786	0.000	0.214	1.00	-0.108
C1 Control (standardized)	F	1.000	0.000	1.000	0.000	0.000		
	M	1.000	0.000	1.000	0.000	0.000		

	Total	1.000	0.000	1.000	0.000	0.000	-	-
C2 Selected (non-standardized)	F	1.000	0.000	1.000	0.000	0.000		
	M	1.000	0.000	1.000	0.000	0.000		
	Total	1.000	0.000	1.000	0.000	0.000	-	-
Total		0.946	0.054	0.897	0.003	0.100	1.00	

1-A 12 bp deletion (D_2 allele) in exon 21 of the IGF-1R gene.

Table 7. Pairwise comparison of the lines for allele frequency (above diagonal) and genotype frequency (below diagonal) for site D in breeder mice.

Line	SA1	SU1	C1	C2
SA1	-	0.305	0.000	0.000
SU1	0.218	-	0.000	0.000
C1	0.000	0.000	-	1.000
C2	0.000	0.000	1.000	-

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Table 8. Distribution of allele and genotype frequencies of the deletion[1] at the IGF-1R locus (site D) in juveniles, test for Hardy-Weinberg equilibrium and F_{IS} estimates by line.

Line	Allele frequency		Genotype frequency			No. of mice	H-W prob.	F_{IS}
	D_1	D_2	D_1D_1	D_2D_2	D_1D_2			
SA1	0.804	0.196	0.714	0.107	0.179	28	0.04	0.449
SA2	0.804	0.196	0.652	0.044	0.304	23	1.00	0.055

SU1	0.900	0.100	0.800	0.000	0.200	20	1.00	-0.086
SU2	0.808	0.192	0.615	0.000	0.385	26	0.54	-0.220
C1	1.000	0.000	1.000	0.000	0.000	27	-	-
C2	1.000	0.000	1.000	0.000	0.000	25	-	-
	0.886	0.114	0.799	0.027	0.174	149	0.46	0.083

Table 9. Pairwise comparison of the lines for allele frequency (above diagonal) and genotype frequency (below diagonal) for site D in juvenile mice.

Line	SA1	SA2	SU1	SU2	C1	C2
SA1	-	1.000	0.257	1.000	0.000	0.001
SA2	1.000	-	0.261	1.000	0.001	0.001
SU1	0.333	0.250	-	0.261	0.031	0.036
SU2	1.000	1.000	0.211	-	0.001	0.001
C1	0.005	0.001	0.029	0.000	-	1.000
C2	0.005	0.001	0.032	0.000	1.000	-

5 Table 10. Distribution of haplotype and genotype frequencies for the joint A and D sites in breeder mice, test for Hardy-Weinberg equilibrium and F_{IS} estimates by line and sex.

Line	Sex	Haplotype frequency	Genotype frequency	H-W	

		$A_1 D_1$	$A_1 D_2$	$A_2 D_1$	$A_1A_1 D_1D_1$	$A_1A_1 D_2D_2$	$A_1A_1 D_1D_2$	$A_2A_2 D_1D_1$	$A_1A_2 D_1D_1$	$A_1A_2 D_1D_2$	prob	F_{IS}
SA1	F	0.444	0.204	0.352	0.185	0.000	0.222	0.111	0.296	0.185		
	M	0.466	0.138	0.396	0.172	0.034	0.172	0.172	0.414	0.034		
	Total	0.455	0.169	0.375	0.179	0.018	0.196	0.143	0.357	0.107	0.82	-0.051
SU1	F	0.810	0.071	0.119	0.667	0.000	0.143	0.047	0.143	0.000		
	M	0.667	0.143	0.190	0.429	0.000	0.190	0.000	0.286	0.095		
	Total	0.738	0.107	0.155	0.547	0.000	0.167	0.024	0.214	0.048	0.90	-0.009
C1	F	0.488	0.000	0.512	0.190	0.000	0.000	0.214	0.595	0.000		
	M	0.476	0.000	0.524	0.262	0.000	0.000	0.310	0.428	0.000		
	Total	0.482	0.000	0.518	0.226	0.000	0.000	0.262	0.512	0.000	1.00	-0.019
C2	F	0.700	0.000	0.300	0.500	0.000	0.000	0.100	0.500	0.000		
	M	0.641	0.000	0.357	0.436	0.000	0.000	0.154	0.410	0.000		
	Total	0.671	0.000	0.329	0.468	0.000	0.000	0.127	0.405	0.000	0.45	0.089
Total		0.575	0.054	0.371	0.341	0.004	0.069	0.157	0.399	0.031	0.98	

Table 11. Pairwise comparison of the lines for haplotype frequency (above diagonal) and genotype frequency (below diagonal) for joint A and D sites in breeder mice.

Line	SA1	SU1	C1	C2
SA1	-	0.000	0.000	0.000
SU1	0.000	-	0.000	0.000
C1	0.000	0.000	-	0.000
C2	0.000	0.000	0.001	-

Table 12. Distribution of haplotype and genotype frequencies for the joint A and D sites in juveniles, test for Hardy-Weinberg equilibrium and F_{IS} estimates by line.

Lines	Haplotype frequency			Genotype frequency						H-W prob.	F_{IS}
	$A_1 D_1$	$A_1 D_2$	$A_2 D_1$	A_1A_1 D_1D_1	A_1A_1 D_2D_2	A_1A_1 D_1D_2	A_2A_2 D_1D_1	A_1A_2 D_1D_1	A_1A_2 D_1D_2		
SA1	0.357	0.196	0.446	0.21	0.11	0.00	0.25	0.25	0.14	0.04	0.341
SA2	0.283	0.196	0.522	0.09	0.00	0.00	0.22	0.35	0.26	0.63	-0.048
SU1	0.725	0.100	0.175	0.55	0.00	0.20	0.10	0.15	0.00	0.17	0.218
SU2	0.692	0.192	0.115	0.46	0.00	0.31	0.00	0.15	0.08	0.68	-0.125
C1	0.481	0.000	0.519	0.22	0.00	0.00	0.26	0.52	0.00	1.00	-0.022
C2	0.620	0.000	0.380	0.48	0.00	0.00	0.24	0.28	0.00	0.08	0.423
Total	0.520	0.114	0.366	0.33	0.00	0.09	0.18	0.29	0.08	0.16	0.135

Table 13. Pairwise comparison of the lines for haplotype frequency (above diagonal) and genotype frequency (below diagonal) for joint A and D sites in juveniles.

Line	SA1	SA2	SU1	SU2	C1	C2
SA1	-	0.696	0.001	0.000	0.001	0.001
SA2	0.749	-	0.000	0.000	0.001	0.000
SU1	0.008	0.001	-	0.415	0.000	0.010

SU2	0.001	0.000	0.442	-	0.000	0.000
C1	0.005	0.001	0.000	0.000	-	0.171
C2	0.003	0.000	0.018	0.000	0.217	-

Example 2
Identification of Polymorphisms in the IGF-1R Gene in a Line of Pigs for the Development of DNA

Animals from a single commercial operation were used to find polymorphisms in candidate genes for reproductive longevity in pigs. Sourcing all animals from a single farm should ensure a similar environment for both high and low reproductive longevity groups. Five living sows with very high parity numbers were chosen as representing high reproductive longevity and five animals culled for reproductive reasons at low parity numbers were chosen as representing low reproductive longevity.

DNA was extracted from tissue samples from these 10 animals and the DNA used to amplify regions of candidate genes using PCR. PCR primers were designed from pig DNA sequence, or from exonic sequence of the homologous gene in other species such as mouse or human. The DNA sequence of these PCR products was then determined and the sequences compared to identify any polymorphisms. Each polymorphism was then assayed over a larger sample of animals from the same commercial population to look for evidence of association with increased reproductive longevity.

Five polymorphisms were found. Of these five, 2 were in intron 16 (SNP16i27 and SNP16i73); one in exon 8 (SNP1772); one in exon 16 (SNP3085); and one in exon 21 (SNP3757).

The polymorphism designated SNP1772, was characterized as a G/A SNP. It is a *TaqI* RFLP. Polymorphism SNP16i27 (position 27 from the end of exon 16) is a G/A SNP. It is an *AvaII* RFLP. SNP16i73 (position 73 from the end of exon 16) is a G/C SNP. It is a *MnlI* RFLP.

PCR-RFLP Protocol for SNP16i27

Primers used in RLFP analysis were as follow:
Primer 16 5' – CCT CCG TGA TGA AGG AGT TC – 3' (SEQ ID NO:14)
Primer 17 5' – TCA GTT CCA TGA TGA CCA GC – 3' (SEQ ID NO:15)

PCR was carried out using the following conditions:

10X PCR Buffer	1.0 ul
2mM dNTPs	1.0 ul
25mM $MgCl_2$	1.0 ul
5uM Primer 16	1.0 ul
5uM Primer 17	1.0 ul
Amplitaq Gold	0.1 ul
QH_2O	3.9 ul
DNA	1.0 ul

Thermal Cycling conditions on the PE9700 were as follow:
94°C – 12 min

94°C – 30 sec
58°C – 30 sec
72°C – 30 sec
(repeated for 39 additional cycles)

72°C – 7 min
4°C – hold

Digested with *Ava*II restriction endonuclease.

The expected product sizes were: allele 1: 141, 122, 44; allele 2: 122, 81, 60, 44.

PCR-RFLP Protocol for SNP16i73

Primers used in RLFP analysis were as follow:
Primer 16 5' – CCT CCG TGA TGA AGG AGT TC – 3' (SEQ ID NO:16)
Primer 17 5' – TCA GTT CCA TGA TGA CCA GC – 3' (SEQ ID NO:17)

PCR was carried out using the following conditions:

10X PCR Buffer	1.0 ul
2mM dNTPs	1.0 ul
25mM $MgCl_2$	1.0 ul
5uM Primer 16	1.0 ul
5uM Primer 17	1.0 ul
Amplitaq Gold	0.1 ul
QH_2O	3.9 ul
DNA	1.0 ul

Thermal Cycling conditions on the PE9700
94°C – 12 min

94°C – 30 sec
58°C – 30 sec
72°C – 30 sec
(repeat for 39 additional cycles)

72°C – 7 min
4°C – hold

Digested with *MnlI* restriction endonuclease.

The expected product sizes were: allele 1: 241, 55, 11; allele 2: 137, 104, 55, 11.

PCR-RFLP Protocol for SNP1772

Primers used in RLFP analysis were as follow:
Primer 9 5' – GGA GTA TGA TGG GCA GGA T – 3' (SEQ ID NO:18)
Primer 8 5' – GAA GCA TTG GTG CGA ATG TA – 3' (SEQ ID NO:19)

PCR was carried out using the following conditions:

10X PCR Buffer	1.0 ul
2mM dNTPs	1.0 ul
25mM $MgCl_2$	0.6 ul
5uM Primer 9	1.0 ul
5uM Primer 8	1.0 ul
Amplitaq Gold	0.1 ul
QH_2O	4.3 ul
DNA	1.0 ul

Thermal Cycling conditions on the PE9700
94°C – 12 min

94°C – 30 sec
56°C – 30 sec
72°C – 30 sec
(repeat for 39 additional cycles)

72°C – 7 min
4°C – hold
Digested with *TaqI* restriction endonuclease.

The expected product sizes were: allele 1: 219; allele 2: 135, 84.

Example 3
SNP 3832

Samples from old surviving sows and from young sows culled during the first 4 parities.

996 sows from four different farms were genotyped and tested for the effect of SNP 3832 on the number of parities. Allele "2" was found to be positively associated with longevity. In average sows of the 22, 12 and 11 genotypes were culled after 7.4, 6.7 and 5.1 parities, respectively. The additive effect of SNP 3832 was estimated to be 1.11/parities/allele (P=0.004) with no dominance effect. The effect is significant, but over estimated due to the data structure.

Germany (GER): Longevity (reproduction) data from sows with known pedigree with DNA samples from their sires.

Data of over 19,000 sows, daughters of 179 sires were used in the analysis. Each sire had at least 50 daughters. There are 76 litter farms represented and the litters were from 1996 to 2001. Phenotypic performance of each sire was estimated based on the daughters' performances, and genotypic data was collected for the sires. Allele "2" found to be positively associated with longevity. SNP 3832estimated additive effect represent a contrast between homozygous sows of 38 days to culling (P=0.062).

A large number of animals were genotyped for the SNP 3832 marker. Animals carrying two copies of the "2" allele (homozygous) are expected to produce more parities and stay in the herd longer.

PCR for SNP 3832

Primer 22 5' - AAG ATG AGG CCT TCC TT - 3' (SEQ ID NO:21)
Primer 23 5' - GAT CAG CAG GTC GAG GAC TG - 3' (SEQ ID NO:22)

PCR Conditions:

10X PCR Buffer	1.0 ul
2mM dNTPs	1.0 ul
25mM MgCl2	0.6 ul
5uM Primer 22	1.0 ul
5uM Primer 23	1.0 ul
Amplitaq Gold	seem to 0.1 ul
QH2O	4.3 ul
DNA	1.0 ul

Thermal Cycling conditions on the PE9700
94°C - 12 min

94°C - 30 sec
58°C - 30 sec
72°C - 1 min
(repeat for 34 additional cycles)

72°C - 7 min
4°C - hold

Digest with *FokI*

Expected product sizes: allele 1: 347; allele 2: 292, 55.

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What is claimed is:

1. A method for genetically identifying an animal with respect to its potential to reproductive longevity comprising:

obtaining a sample of genetic material from an animal; and

assaying for the presence of a polymorphism in the insulin-like growth factor 1 receptor gene (IGF-1R), wherein the polymorphism is associated with reproductive longevity.

2. The method of claim 1 wherein said polymorphism is selected from the group consisting of: a single nucleotide polymorphism (SNP), a deletion, and an insertion.

3. The method of claim 1 wherein the animal is selected from a group consisting of: a mouse ,a pig, and a cow.

4. The method of claim 1 wherein a step of assaying the polymorphism is selected from the group consisting of: direct sequencing, restriction fragment length polymorphism (RFLP) analysis, single-stranded conformation polymorphism (SSCP), PCR amplification of specific alleles, amplification of DNA target by PCR followed by a mini-sequencing assay, allelic discrimination during PCR, Genetic Bit Analysis, Pyrosequencing, oligonucleotide ligation assay, and analysis of melting curves.

5. The method of claim 4 wherein the step of assaying the polymorphism is RFLP.

6. The method of claim 4 wherein the step of assaying the polymorphism is SSCP.

7. The method of claim 1 wherein the step of assaying for the presence of the polymorphism comprises the steps of:

digesting the genetic material with a restriction endonuclease that cleaves the gene in at least one place, wherein a particular restriction endonuclease pattern indicates the presence or absence of a polymorphism;

separating the fragments obtained from the digestion;

detecting a restriction pattern generated by the fragments; and

comparing the pattern with a second restriction pattern for the gene obtained by using the restriction endonuclease, wherein the second restriction pattern is associated with reproductive longevity.

8. The method of claim 7 wherein said separation is by gel electrophoresis.

9. The method of claim 7 further comprising:

amplifying the gene or a portion thereof which contains at least one polymorphism, prior to digestion.

10. The method of claim 9 wherein the amplification includes selecting a forward and a reverse sequence primer capable of amplifying a region of the gene which contains a polymorphism.

11. The method of claim 1 wherein the polymorphism is identified as an A to G nucleotide substitution at position 3876 of the gene.

12. The method of claim 1 wherein the polymorphism is identified as a G to A nucleotide substitution at position 331 of the gene.

13. The method of claim 1 wherein the polymorphism is a 12 base pair deletion at positions 3896-3907 of the gene.

14. The method of claim 7 wherein the restriction endonuclease is *HpaII*.

15. The method of claim 7 wherein the restriction endonuclease *DpnII*.

16. The method of claim 7 wherein the restriction endonuclease is *TaqI*.

17. The method of claim 7 wherein the restriction endonuclease is *MnlI*.

18. The method of claim 7 wherein the restriction endonuclease is *AvaII*.

19. The method of claim 10 wherein the forward primer is SEQ ID NO:8 and wherein the reverse primer is SEQ ID NO:9.

20. The method of claim 10 wherein the forward primer is SEQ ID NO:10 and wherein the reverse primer is SEQ ID NO:11.

21. The method of claim 10 wherein the forward primer is SEQ ID NO:12 and wherein the reverse primer is SEQ ID NO:13.

22. The method of claim 10 wherein the forward primer is SEQ ID NO:14 and wherein the reverse primer is SEQ ID NO:15.

23. The method of claim 10 wherein the forward primer is SEQ ID NO:16 and wherein the reverse primer is SEQ ID NO:17.

24. The method of claim 10 wherein the forward primer is SEQ ID NO:18 and wherein the reverse primer is SEQ ID NO:19.

25. A method of screening animals to determine those more likely to have reproductive longevity, the method comprising:

obtaining a biological sample from an animal; and

assaying for the presence of a genotype in the IGF-1R gene, wherein the genotype is associated with reproductive longevity and characterized by a restriction fragment pattern, wherein said pattern when compared to a second restriction pattern is known to have or not have a desired polymorphic marker, the presence of said marker being indicative of an animal more likely to have reproductive longevity.

26. The method of claim 25 wherein the assaying step comprises amplifying the gene or a region thereof containing the marker with a forward and a reverse sequence primer.

27. The method of claim 26 wherein the forward primer is SEQ ID NO:8 and the reverse primer is SEQ ID NO:9.

28. The method of claim 26 wherein the forward primer is SEQ ID NO:10 and the reverse primer is SEQ ID NO:11.

29. The method of claim 26 wherein the forward primer is SEQ ID NO:12 and said reverse primer is SEQ ID NO:13.

30. The method of claim 26 wherein the forward primer is SEQ ID NO:14 and the reverse primer is SEQ ID NO:15.

31. The method of claim 26 wherein the forward primer is SEQ ID NO:16 and the reverse primer is SEQ ID NO:17.

32. The method of claim 26 wherein the forward primer is SEQ ID NO:18 and the reverse primer is SEQ ID NO:19.

33. The method of claim 25 wherein the marker is *DpnII*.

34. The method of claim 25 wherein the marker is *HpaII*.

35. The method of claim 25 wherein the marker is *TaqI*.

36. The method of claim 25 wherein the marker is *MnlI*.

37. The method of claim 25 wherein the marker is *AvaII*.

38. The method of claim 33 wherein a G to A nucleotide substitution results in a restriction pattern characterized by a 328 nucleotide fragment, a 125 nucleotide fragment, and a 32 nucleotide fragment.

39. The method of claim 34 wherein an A to G nucleotide substitution results in a restriction pattern characterized by a 373 nucleotide fragment, a 134 nucleotide fragment, and a 127 nucleotide fragment.

40. The method of claim 34 wherein the deletion is characterized by a 12 bp fragment having SEQ ID NO:20 appearing once in the IGF-1R gene.

41. The method of claim 35 wherein a G to A nucleotide substitution results in a restriction pattern characterized by a 135 nucleotide fragment and an 84 nucleotide fragment.

42. The method of claim 36 wherein an G to C nucleotide substitution results in a restriction pattern characterized by a 137 nucleotide fragment, a 104 nucleotide fragment, a 55 nucleotide fragment, and an 11 nucleotide fragment.

43. The method of claim 37 wherein an G to A nucleotide substitution results in a restriction pattern characterized by a 122 nucleotide fragment, an 81 nucleotide fragment, a 60 nucleotide fragment, and a 44 nucleotide fragment.

44. The method of claim 25 wherein said animal is selected from the group consisting of: a pig and a mouse.

45. A method for screening animals to determine those more likely to exhibit favorable traits associated with reproductive longevity, said method comprising:
obtaining a genetic sample from an animal; and
detecting the presence or absence of at least one allele in the IGF-1R gene wherein the presence of the allele is predictive of the animal having reproductive longevity.

46. The method of claim 45 wherein the allele is defined in intron 16 of the gene.

47. The method of claim 45 wherein the allele is defined in exon 21 at position 3876 of the gene.

48. The method of claim 45 wherein the allele is defined in exon 21 at positions 3896-3907 of the gene.

49. The method of claim 45 wherein the allele is defined at position 27 at the end of intron 16 of the gene.

50. The method of claim 45 wherein the allele is defined at position 73 at the end of intron 16 of the gene.

51. The method of claim 45 wherein the animal is selected from a group consisting of: a pig and a mouse.

52. A method for determining the haplotype of the IGF-1R gene of an animal comprising:

obtaining a genetic sample from an animal; and

analyzing the genetic sample for the presence of an IGF-1R gene A_1D_1, A_1D_2, or A_2D_1 haplotype allele, wherein the haplotype effects reproductive performance or the ability to sustain stress factors.

53. The method of claim 52 wherein the A_1D_1 allele is indicative of having a favorable effect on lactation and pregnancy stress.

54. The method of claim 52 wherein the A_1D_2 allele is indicative of having a negative effect on reproductive performance.

55. The method of claim 52 wherein the A_2D_1 allele is indicative of reproductive longevity.

56. The method of claim 52 wherein the animal is a mouse.

57. A method for genotyping an animal for reproductive longevity, the method comprising:
obtaining a sample of genetic material from an animal;
detecting a polymorphism in the IGF-1R gene of the animal;
determining whether the animal possesses a marker, wherein the marker is indicative of the animal having two copies of allele 2.

58. The method of claim 57 wherein the step of detecting the polymorphism comprises:
digesting amplified nucleic acid with a restriction enzyme; and
separating the nucleic acid fragments according to size such that a restriction fragment pattern is generated,
wherein the restriction fragment pattern generated is indicative of an animal reproductive longevity.

59. The method of claim 57 wherein prior to digesting the nucleic acid with a restriction enzyme, amplifying the nucleic acid with a forward primer and a reverse primer.

60. The method of claim 59 wherein the forward and reverse primer is SEQ ID NO:21 and SEQ ID NO:22.

61. The method of claim 57 wherein the restriction enzyme is *FokI*.

62. The method of claim 58 wherein the restriction pattern characterized by a 295 nucleotide fragment, and a 55 nucleotide fragment.

63. The method of claim 57 wherein the marker is positively associated with longevity.

64. The method of claim 57 wherein the animal is a pig.

65. A method for genetically identifying an animal comprising:
obtaining a sample of genetic material from an animal; and
assaying for the presence of a genotype in the IGF-1R gene sequence as set forth in SEQ ID NO:1 or a region thereof in the sample,
wherein the animal possesses a nucleic acid sequence having at least 95% sequence identity to SEQ ID NO:1 or a fragment thereof.

66. The method of claim 65 wherein the polymorphism is identified by a G to A nucleotide substitution in intron 16.

67. The method of claim 65 wherein the polymorphism is identified by an A to G nucleotide substitution in exon 21.

68. The method of claim 65 wherein the polymorphism is identified as a 12 bp deletion in exon 21.

69. The method of claim 65 wherein the polymorphism is identified as an insertion of a G nucleotide in intron 16 at position 176.

70. The method of claim 65 wherein the animal is a mouse.

71. A method for genetically identifying an animal comprising:
obtaining a sample of genetic material from an animal; and
assaying for the presence of a genotype in the IGF-1R gene sequence as set forth in SEQ ID NO:7 or a region thereof in the sample,
wherein the animal posses a nucleic acid sequence having at least 95% sequence identity to SEQ ID NO:7 or a fragment thereof.

72. The method of claim 71 wherein said polymorphism is identified as a G to A nucleotide substitution in intron 16.

73. The method of claim 71 wherein said polymorphism is identified as a G to C nucleotide substitution in intron 16.

74. The method of claim 71 wherein said polymorphism is identified as a G to A nucleotide substitution in exon 8.

75. The method of claim 71 wherein the animal is a pig.

76. The method of claim 65 wherein the polymorphism is an A to G nucleotide substitution in exon 21 at position 3876.

77. The method of claim 65 wherein the polymorphism is a 12 bp deletion in exon 21 at positions 3896-3907.

78. The method of claim 71 wherein said polymorphism is a G to A nucleotide substitution at position 27 from the end of intron 16.

79. The method of claim 71 wherein said polymorphism is a G to C nucleotide substitution at position 73 from the end of intron 16.

80. A method for genetically identifying cattle with respect to its potential to reproductive longevity comprising:
obtaining a sample of genetic material from a cow; and
assaying for the presence of a polymorphism in the insulin-like growth factor 1 receptor gene (IGF-1R), wherein the polymorphism is associated with reproductive longevity.

ABSTRACT OF THE DISCLOSURE

Disclosed herein are embodiments for genotyping an animal for the presence of polymorphic alleles in the IGF-1R gene that are associated with reproductive longevity and/or ability to better sustain stress, and preferably selecting those animals for future breeding purposes.

Application Data Sh t

Application Information

Application Type::	Regular
Subject Matter::	Utility
Sequence submission?::	Yes
Computer Readable Form (CRF)?::	Yes
Number of copies of CRF::	1
Title:	INSULIN-LIKE GROWTH FACTOR-1 RECEPTOR (IGF-1R) POLYMORPHIC ALLELES AND USE OF THE SAME TO IDENTIFY DNA MARKERS FOR REPRODUCTIVE LONGEVITY
Attorney Docket Number::	P05562US00
Request for Early Publication::	No
Request for Non-Publication::	No
Total Drawing Sheets::	83
Small Entity?::	No
Petition included?::	No

Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	Canadian
Status::	Full Capacity
Given Name::	ABDOL
Middle Name::	HOSSAIN
Family Name::	FARID
City of Residence::	Truro
State or Province of Residence::	Nova Scotia
Country of Residence::	Canada
Street of mailing address::	18 Heritage Place
City of mailing address::	Truro

State or Province of mailing address::	Nova Scotia
Country of mailing address::	Canada
Postal or Zip Code of mailing address::	B2N 6J4
Applicant Authority Type::	Inventor
Primary Citizenship Country::	Kenya
Status::	Full Capacity
Given Name::	CHARLES
Middle Name::	J.
Family Name::	OTIENO
City of Residence::	Ames
State or Province of Residence::	Iowa
Country of Residence::	USA
Street of mailing address::	2125 Prairie View West, Apt. 102
City of mailing address::	Ames
State of mailing address::	Iowa
Country of mailing address::	USA
Postal or Zip Code of mailing address::	50010
Applicant Authority Type::	Inventor
Primary Citizenship Country::	Canadian
Status::	Full Capacity
Given Name::	BERNHARD
Middle Name::	FRANZ
Family Name::	BENKEL
City of Residence::	Lethbridge
State or Province of Residence::	Alberta
Country of Residence::	Canada
Street of mailing address::	19 Wildwood Rd. West

Initial 9/15/03

City of mailing address::	Lethbridge
State or Province of mailing address::	Alberta
Country of mailing address::	Canada
Postal or Zip Code of mailing address::	T1K 6C2

Correspondence Information

Correspondence Customer Number::	22885
Name::	McKee, Voorhees & Sease, P.L.C.
Street of mailing address::	801 Grand Avenue, Suite 3200
City of mailing address:	Des Moines
State of mailing address:	Iowa
Country of mailing address::	USA
Postal Zip Code or mailing address::	50309-2721
Phone number::	515-288-3667
Fax number::	515-288-1338
E-Mail Address::	patatty@ipmvs.com

Representative Information

Representative Customer Number::	22885	

Assignment Information

Assignee name::

Street of mailing address::

City of mailing address::

State or Province of
mailing address::

Country of mailing address::

Postal or Zip Code of
mailing address::

Initial 9/15/03

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   1 atgaagtctg gctccggagg agggtccccg acctcgctgt gggggctcgt gtttctctcc
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 541 ctgtgtccag ggacattgga ggagaagccc atgtgtgaga agaccaccat caacaatgag
 601 tacaactacc gctgctggac cacaaatcgc tgccagaaaa tgtgcccaag tgtgtgcggg
 661 aagcgagcct gcaccgagaa caacgagtgc tgccacccgg agtgcctggg cagctgccac
 721 acaccggacg acaacacaac ctgcgtggcc tgcagacact actactacaa aggcgtgtgt
 781 gtgcctgcct gcccgcctgg cacctacagg ttcgagggct ggcgctgtgt ggatcgcgat
 841 ttctgcgcca acatccccaa cgctgagagc agtgactcgg atggcttcgt tatccacgac
 901 gatgagtgca tgcaggagtg tccctcaggc ttcatccgca acagcaccca gagcatgtac
 961 tgtatccgct gcgaaggccc ctgccccaaa gtctgcggcg atgaagagaa gaaaacgaaa
1021 accatcgatt cggtgacttc tgctcaaatg ctccaaggat gcaccatcct gaagggcaat
1081 ctgcttatta acatccggag aggcaataac attgcctcgg agttggagaa cttcatgggg
1141 ctcatcgagg tggtgaccgg ctacgtgaag atccgccatt ctcatgcctt ggtctccttg
1201 tccttcctga agaaccttcg tctcatctta ggagaggagc agctggaagg gaactactcc
1261 ttctatgtcc tagacaacca gaacttgcag cagctgtggg actggaacca ccggaacctg
1321 accgtcaggt ccggaaagat gtactttgct ttcaatccca agctgtgtgt ctccgaaatt
1381 taccgcatgg aggaagtgac cggaaccaag ggacgccaga gcaaagggga cataaacacc
1441 aggaacaacg gagagcgagc ttcctgtgaa agtgatgttc tccgtttcac ctccaccacg
1501 acctggaaga accgaatcat cataacgtgg caccggtacc ggccgccgga ctaccgggat
1561 ctcatcagct tcacagttta ctacaaggag gcaccattta aaaacgttac ggaatatgac
1621 gggcaggatg cctgtggctc caacagctgg aacatggtgg atgtagacct gcctccgaac
1681 aaggagggcg agcctggcat tttactgcat gggctgaagc cctggaccca gtatgctgtc
1741 tatgtcaagg ctgtgaccct caccatggtg gaaaacgacc atatccgtgg ggccaaaagt
1801 gaaatcttgt acattcgcac caatgcttca gtcccttcca ttcccctaga tgtcctctca
1861 gcatcaaact cttcctctca gctgattgtg aagtggaatc ctccaactct gcccaatggt
1921 aacttgagtt actacattgt gaggtggcag cggcagcccc aggatggtta cctgtaccgg
1981 cacaactact gctccaaaga caaaataccc atcagaaagt acgccgatgg taccatcgac
2041 gtggaggagg tgacggaaaa tcccaagaca gaagtgtgtg gtggtgataa agggccatgc
2101 tgcgcttgcc ctaaaactga agctgagaag caggctgaga aggaggaggc tgagtaccgt
2161 aaagtctttg agaatttcct tcacaattcc atctttgtgc ccaggcccga aaggaggcgg
2221 agagacgtca tgcaagtggc caacacgacc atgtccagcc gaagcaggaa caccacggta
2281 gctgacacct acaatatcac agacccggag gagttcgaga cagagtaccc tttctttgag
2341 agcagagtgg ataacaagga gaggactgtc atctccaacc tccggccttt cactctgtac
2401 cgcatcgata tccacagctg caaccacgag gctgagaagc tgggctgcag cgcctccaac
2461 ttcgtctttg cgagaaccat gccagcagaa ggagcagatg atatccctgg tccggtgacc
2521 tgggagccaa gacccgaaaa ctccatcttt ttaaagtggc cagaacccga gaaccccaac
2581 ggattgatcc taatgtatga aattaaatac gggtcgcaag tcgaggatca gcgggaatgt
2641 gtgtccagac aggagtacag gaagtacgga ggggccaaac tcaaccgtct aaacccaggg
2701 aactatacag cccggattca ggctacctcc ctctctggga atgggtcatg gacagatcct
2761 gtgttcttct atgtccccgc caaaacgacg tatgagaact tcatgcatct gatcattgct
2821 ctgccggttg ccatcctgct gatcgttggg gggctggtta tcatgctgta tgtcttccat
```

FIGURE 1A

2881 agaaagagaa ataacagcag gttgggcaat ggagtgctgt atgcttctgt gaaccccgag
2941 tatttcagcg cagctgatgt gtacgtgcct gatgaatggg aggtagctcg agagaagatc
3001 accatgaacc gggagctcgg acaagggtcc tttgggatgg tctatgaagg agtggccaag
3061 ggtgtggtca aggatgaacc cgaaaccaga gtggccatca agacggtaaa cgaggctgca
3121 agtatgcgtg aaagaatcga gtttctcaac gaggcctcgg tgatgaagga gttcaattgt
3181 caccatgtgg tccggttgct gggtgtggta tcccaaggcc agcccaccct ggtcatcatg
3241 gaactaatga cacgcggtga tctcaaaagt tatctccggt ctctgaggcc agaagtggag
3301 cagaataatc tagtcctcat tcctccgagc ttaagcaaga tgatccagat ggctggagag
3361 attgcagatg gcatggccta cctcaatgcc aacaagttcg tccacagaga ccttgctgct
3421 aggaactgca tggtagccga agatttcaca gtcaaaattg gagatttcgg tatgacacga
3481 gacatctacg agacggacta ctaccggaaa ggcgggaagg gtttgctgcc tgtgcgctgg
3541 atgtctcccg agtccctcaa ggatggtgtc ttcactactc attctgatgt ctggtccttc
3601 ggggtcgtcc tctgggagat cgccacgctg gctgagcagc cctaccaggg cttgtccaac
3661 gagcaagttc ttcgtttcgt catggagggt ggccttctgg acaagccgga caactgccct
3721 gatatgctgt ttgaacttat gcgcatgtgc tggcagtata accccaagat gcggccctcc
3781 ttcctggaga tcatcggcag catcaaggat gagatggagc ccagcttcca ggaggtctcc
3841 ttctactaca gcgaggagaa caagcctccc gagccagagg agctggagat ggagctggag
3901 atggagcctg agaacatgga gagcgtccca ctggaccctt cggcctcctc agcctccctg
3961 cctctgcctg aaagacactc aggacacaag gctgagaatg gcccgggccc tggcgtgctc
4021 gttctccgcg ccagttttga tgagagacag ccttacgctc acatgaacgg gggacgcgcc
4081 aacgagaggg ccttgcctct gccccagtcc tcgacctgct gatcctcgga cacaccgaag
4141 cacgcgccaa cagtaacgtg tgtgccccac tcggtgggcg gggggggcggg gaggggagag
4201 caggttgtaa caatctattc acaagcctcc tgtacctcag tggatcttca gacctgccat
4261 tgctgcccac gggagacggc ttctctgcag taaacacatt tgggaccttc ctttttttcaa
4321 tatgcaagca gctttttatt tcctttaccc gaacccttaa ctgacatggg cctctgcaaa
4381 ccttaatgac aacacttaat agcaacagga cactcgagaa ttgagtctct tcgttctctg
4441 cctttttctc tcctctgcct tccctctctg ccctctcccc ttccacttcc acgctctcct

FIGURE 1B

```
   1 mksgsgggsp tslwglvfls aalslwptsg eicgpgidir ndyqqlkrle nctviegflh
  61 illiskaedy rsyrfpkltv iteylllfrv agleslgdlf pnltvirgwk lfynyalvif
 121 emtnlkdigl ynlrnitrga irieknadlc ylstidwsli ldavsnnyiv gnkppkecgd
 181 lcpgtleekp mcekttinne ynyrcwttnr cqkmcpsvcg kractennec chpeclgsch
 241 tpddnttcva crhyyykgvc vpacppgtyr fegwrcvdrd fcanipnaes sdsdgfvihd
 301 decmqecpsg firnstqsmy cipcegpcpk vcgdeekktk tidsvtsaqm lqgctilkgn
 361 llinirrgnn iaselenfmg lievvtgyvk irhshalvsl sflknlrlil geeqlegnys
 421 fyvldnqnlq qlwdwnhrnl tvrsgkmyfa fnpklcvsei yrmeevtgtk grqskgdint
 481 rnngerasce sdvlrftstt twknriiitw hryrppdyrd lisftvyyke apfknvteyd
 541 gqdacgsnsw nmvdvdlppn kegepgillh glkpwtqyav yvkavtltmv endhirgaks
 601 eilyirtnas vpsipldvls asnsssqliv kwnpptlpng nlsyyivrwq rqpqdgylyr
 661 hnycskdkip irkyadgtid veevtenpkt evcggdkgpc cacpkteaek qaekeeaeyr
 721 kvfenflhns ifvprperrr rdvmqvantt mssrsrnttv adtynitdpe efeteypffe
 781 srvdnkertv isnlrpftly ridihscnhe aeklgcsasn fvfartmpae gaddipgpvt
 841 weprpensif lkwpepenpn glilmyeiky gsqvedqrec vsrqeyrkyg gaklnrlnpg
 901 nytariqats lsgngswtdp vffyvpaktt yenfmhliia lpvaillivg glvimlyvfh
 961 rkrmnsrlgn gvlyasvnpe yfsaadvyvp dewevareki tmnrelgqgs fgmvyegvak
1021 gvvkdepetr vaiktvneaa smreriefln easvmkefnc hhvvrllgvv sqgqptlvim
1081 elmtrgdlks ylrslrpeve qnnlvlipps lskmiqmage iadgmaylna nkfvhrdlaa
1141 rncmvaedft vkigdfgmtr diyetdyyrk ggkgllpvrw mspeslkdgv ftthsdvwsf
1201 gvvlweiatl aeqpyqglsn eqvlrfvmeg glldkpdncp dmlfelmrmc wqynpkmrps
1261 fleiigsikd emepsfqevs fyyseenkpp epeelemele mepenmesvp ldpsassasl
1321 plperhsghk aengpgpgvl vlrasfderq pyahmnggra neralplpqs stc
```

FIGURE 2

```
   1 gctcattcat ttccactccg catttctgcc cctcgccggc ctcgcccgcg cccgggactt
  61 cggaccagtc tcgccaactg cgtcgcgctc tcccgccgcg taggctccgg tggtcgttcc
 121 ctccggggat cgggtggcgt ttgtcctcgc ctgcggcgat ttgggctttg ctcctctttc
 181 tgtacagttt tcctccttct tctgcatctc tgcgtttgca aatggaggcc gacgacgccg
 241 acagcccgcc ccggcgcgcc ccggcttccc gactccgccg ccccgtgggc cgctgctgcc
 301 ggcgctgagg ggccgccccg cgccaccctc cttgtccacg ccgctttccg aggatcgtcg
 361 cctgcgctct tgtttttgga cgagagtgag gactgagttg gagacttttt ttttcttttt
 421 ttcttttctt ttttttttt ttttctattt ttgagaaaag ggaatttcgt cccaaataaa
 481 aggaatgaag tctggctccg gaggagggtc cccgacctcg ctgtgggggc tcgtgtttct
 541 ctccgccgcg ctctctctct ggccgacgag tggagaaatc tgtgggcccg gcattgacat
 601 ccgcaacgac tatcagcagc tgaagcgcct ggaaaactgc acggtgatcg agggcttcct
 661 ccacatcctg ctcatctcca aggccgagga ctaccgaagc taccgcttcc ccaagctcac
 721 cgtcatcact gagtacttgc tgctcttccg agtcgctggc ctcgagagcc tgggagacct
 781 cttccccaac ctcacagtca tccgtggctg gaaactcttc tacaactacg cactggtcat
 841 cttcgagatg accaatctca aggatattgg gctttataat ctgaggaaca ttactcgggg
 901 ggccatcagg attgagaaga acgccgacct ctgttacctc tccaccatag actggtctct
 961 catcttggat gcggtgtcca ataactacat tgtggggaac aagccccccga aggaatgtgg
1021 ggacctgtgt ccagggacat tggaggagaa gcccatgtgt gagaagacca ccatcaacaa
1081 tgagtacaac taccgctgct ggaccacaaa tcgctgccag aaaatgtgcc caagtgtgtg
1141 cgggaagcga gcctgcaccg agaacaacga gtgctgccac ccggagtgcc tgggcagctg
1201 ccacacaccg gacgacaaca caacctgcgt ggcctgcaga cactactact acaaaggcgt
1261 gtgtgtgcct gcctgcccgc ctggcaccta caggttcgag ggctggcgct gtgtggatcg
1321 cgatttctgc gccaacatcc ccaacgctga gagcagtgac tcggatggct tcgttatcca
1381 cgacgatgag tgcatgcagg agtgtccctc aggcttcatc cgcaacagca cccagagcat
1441 gtactgtatc ccctgcgaag gcccctgccc caaagtctgc ggcgatgaag agaagaaaac
1501 gaaaaccatc gattcggtga cttctgctca aatgctccaa ggatgcacca tcctgaaggg
1561 caatctgctt attaacatcc ggagaggcaa taacattgcc tcggagttgg agaacttcat
1621 ggggctcatc gaggtggtga ccggctacgt gaagatccgc cattctcatg ccttggtctc
1681 cttgtccttc ctgaagaacc ttcgtctcat cttaggagag gagcagctgg aagggaacta
1741 ctccttctat gtcctagaca accagaactt gcagcagctg tgggactgga accaccggaa
1801 cctgaccgtc aggtccggaa agatgtactt tgctttcaat cccaagctgt gtgtctccga
1861 aatttaccgc atggaggaag tgaccggaac caagggacgc cagagcaaag gggacataaa
1921 caccaggaac aacggagagc gagcttcctg tgaaagtgat gttctccgtt tcacctccac
1981 cacgacctgg aagaaccgaa tcatcataac gtggcaccgg taccggccgc cggactaccg
2041 ggatctcatc agcttcacag tttactacaa ggaggcacca tttaaaaacg ttacggaata
2101 tgacgggcag gatgcctgtg gctccaacag ctggaacatg gtggatgtag acctgcctcc
2161 gaacaaggag ggcgagcctg gcattttact gcatgggctg aagccctgga cccagtatgc
2221 tgtctatgtc aaggctgtga ccctcaccat ggtggaaaac gaccatatcc gtggggccaa
2281 aagtgaaatc ttgtacattc gcaccaatgc ttcagtccct tccattcccc tagatgtcct
2341 ctcagcatca aactcttcct ctcagctgat tgtgaagtgg aatcctccaa ctctgcccaa
2401 tggtaacttg agttactaca ttgtgaggtg gcagcggcag ccccaggatg gttacctgta
2461 ccggcacaac tactgctcca aagacaaaat acccatcaga aagtacgccg atggtaccat
2521 cgacgtggag gaggtgacgg aaaatcccaa gacagaagtg tgtggtggtg ataaagggcc
```

Figure 3A

```
2581 atgctgcgct tgccctaaaa ctgaagctga gaagcaggct gagaaggagg aggctgagta
2641 ccgtaaagtc tttgagaatt tccttcacaa ttccatcttt gtgcccaggc ccgaaaggag
2701 gcggagagac gtcatgcaag tggccaacac gaccatgtcc agccgaagca ggaacaccac
2761 ggtagctgac acctacaata tcacagaccc ggaggagttc gagacagagt acccttttctt
2821 tgagagcaga gtggataaca aggagaggac tgtcatctcc aacctccggc ctttcactct
2881 gtaccgcatc gatatccaca gctgcaacca cgaggctgag aagctgggct gcagcgcctc
2941 caacttcgtc tttgcgagaa ccatgccagc agaaggagca gatgatatcc ctggtccggt
3001 gacctgggag ccaagacccg aaaactccat ctttttaaag tggccagaac ccgagaaccc
3061 caacggattg atcctaatgt atgaaattaa atacgggtcg caagtcgagg atcagcggga
3121 atgtgtgtcc agacaggagt acaggaagta cggaggggcc aaactcaacc gtctaaaccc
3181 agggaactat acagcccgga ttcaggctac ctccctctct gggaatgggt catggacaga
3241 tcctgtgttc ttctatgtcc ccgccaaaac gacgtatgag aacttcatgc atctgatcat
3301 tgctctgccg gttgccatcc tgctgatcgt tgggggggctg gttatcatgc tgtatgtctt
3361 ccatagaaag agaaataaca gcaggttggg caatggagtg ctgtatgctt ctgtgaaccc
3421 cgagtatttc agcgcagctg atgtgtacgt gcctgatgaa tgggaggtag ctcgagagaa
3481 gatcaccatg aaccgggagc tcggacaagg gtcctttggg atggtctatg aaggagtggc
3541 caagggtgtg gtcaaggatg aacccgaaac cagagtggcc atcaagacgg taaacgaggc
3601 tgcaagtatg cgtgaaagaa tcgagtttct caacgaggcc tcggtgatga aggagttcaa
3661 ttgtcaccat gtggtccggt tgctgggtgt ggtatcccaa ggccagccca ccctggtcat
3721 catggaacta atgacacgcg gtgatctcaa aagttatctc cggtctctga ggccagaagt
3781 ggagcagaat aatctagtcc tcattcctcc gagcttaagc aagatgatcc agatggctgg
3841 agagattgca gatggcatgg cctacctcaa tgccaacaag ttcgtccaca gagaccttgc
3901 tgctaggaac tgcatggtag ccgaagattt cacagtcaaa attggagatt tcggtatgac
3961 acgagacatc tacgagacgg actactaccg gaaaggcggg aaggggttgc tgcctgtgcg
4021 ctggatgtct cccgagtccc tcaaggatgg tgtcttcact actcattctg atgtctggtc
4081 cttcggggtc gtcctctggg agatcgccac gctggctgag cagccctacc agggcttgtc
4141 caacgagcaa gttcttcgtt tcgtcatgga gggtggcctt ctggacaagc cggacaactg
4201 ccctgatatg ctgtttgaac ttatgcgcat gtgctggcag tataacccca agatgcggcc
4261 ctccttcctg gagatcatcg gcagcatcaa ggatgagatg gagcccagct tccaggaggt
4321 ctccttctac tacagcgagg agaacaagcc tcccgagcca gaggagctgg agatggagcc
4381 tgagaacatg gagagcgtcc cactggaccc ttcggcctcc tcagcctccc tgcctctgcc
4441 tgaaagacac tcaggacaca aggctgagaa tggcccgggc cctggcgtgc tcgttctccg
4501 cgccagtttt gatgagagac agccttacgc tcacatgaac gggggacgcg ccaacgagag
4561 ggccttgcct ctgccccagt cctcgacctg ctgatcctcg gacacaccga agcacgcgcc
4621 aacagtaacg tgtgtgcgcc cactcggtgg gcgggggggc ggggagggga gagcaggttg
4681 taacaatcta ttcacaagcc tcctgtacct cagtggatct tcagacctgc cattgctgcc
4741 cacgggagac ggcttctctg cagtaaacac atttgggacc ttccttttt caatatgcaa
4801 gcagcttttt atttccttta cccgaaccct taactgacat gggcctctgc aaaccttaat
4861 gacaacactt aatagcaaca ggacactcga gaattgagtc tcttcgttct ctgccttttt
4921 ctctcctctg ccttccctct ctgccctctc cccttccact tccacgctct cct
```

Figure 3B

```
ID 1: 3727    ct0g ttt gaa ctt atg cgc atg tgc tgg cag tat aac ccc aag atg cgg ccc tcc ttc ctg 3786
ID 3: 4211    ct0g ttt gaa ctt atg cgc atg tgc tgg cag tat aac ccc aag atg cgg ccc tcc ttc ctg 4270
aa  : 1243     l   f   e   l   m   r   m   c   w   q   y   n   p   k   m   r   p   s   f   l  1262

ID 1: 3787    gag atc atc ggc agc atc aag gat gag atg gag ccc agc ttc cag gag gtc tcc ttc tac  3846
ID 3: 4271    gag atc atc ggc agc atc aag gat gag atg gag ccc agc ttc cag gag gtc tcc ttc tac  4330
aa  : 1263     e   i   i   g   s   i   k   d   e   m   e   p   s   f   q   e   v   s   f   y  1282

ID 1: 3847    tac agc gag gag aac aag cct ccc gag cca gag gag ctg gag atg gag ctg gag atg gag 3906
ID 3: 4331    tac agc gag gag aac aag cct ccc gag cca gag gag ctg gag atg gag c-- --- --- --- 4379
aa  : 1283     y   s   e   e   n   k   p   p   e   p   e   e   l   e   m   e   l   e   m   e  1302

ID 1: 3907    gct gag aac atg gag agc gtc cca ctg gac cct tcg gcc tcc tca gcc tcc ctg cct ctg 3966
ID 3: 4380    -ct gag aac atg gag agc gtc cca ctg gac cct tcg gcc tcc tca gcc tcc ctg cct ctg 4438
aa  : 1303     p   e   n   m   e   s   v   p   l   d   p   s   a   s   s   a   s   l   p   l  1322

ID 1: 3967    cct gaa aga cac tca gga cac aag gct gag aat ggc ccg ggc cct ggc gtg ctc gtt ctc 4026
ID 3: 4399    cct gaa aga cac tca gga cac aag gct gag aat ggc ccg ggc cct ggc gtg ctc gtt ctc 4498
aa  : 1323     p   e   r   h   s   g   h   k   a   e   n   g   p   g   p   g   v   l   v   l  1342

ID 1: 4027    cgc gcc agt ttt gat gag aga cag cct tac gct cac atg aac ggg gga cgc gcc aac gag 4086
ID 3: 4499    cgc gcc agt ttt gat gag aga cag cct tac gct cac atg aac ggg gga cgc gcc aac gag 4558
aa  :1343      r   a   s   f   d   e   r   q   p   y   a   h   m   n   g   g   r   a   n   e  1362

ID 1: 4087    agg gcc ttg cct ctg ccc cag tcc tcg acc tgc tga  4122
ID 3: 4559    agg gcc ttg cct ctg ccc cag tcc tcg acc tgc tga  4594
aa  : 1363     r   a   l   p   l   p   q   s   s   t   c   *   1373
```

FIGURE 4

```
ID 5: 1      agagtggccatcaagacggtaaacgaggctgcaagtatgcgtgaaagaatcgagtttctc 60
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
ID 6: 56632 agagtggccatcaagacggtaaacgaggctgcaagtatgcgtgaaagaatcgagtttctc 56573

ID 5: 61     aacgaggcctcggtgatgaaggagttcaattgtcaccatgtg0gtaagaagccaagatgag 120
             |||||||||||||||||||||||||||||||||||||||| ||||||||||||||||||
ID 6: 56572 aacgaggcctcggtgatgaaggagttcaattgtcaccatgtg0gtaagaagccaagatgag 56513

ID 5: 121    acatggacagaaagtatggacagaaaggaccaccctgtatgtccttggccagctacggaa 180
             |||||||||||||||||||||||||||||||||||||||||||||||||||||||| |||
ID 6: 56512 acatggacagaaagtatggacagaaaggaccaccctgtatgtccttggccagctac-gaa 56454

ID 5: 181    ttgttgccttgccctcttcccagtgggtagtttccccgttgcattcttgccacccacaga 240
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
ID 6: 56453 ttgttgccttgccctcttcccagtgggtagtttccccgttgcattcttgccacccacaga 56394

ID 5: 241    cccttgaggtgggagcctcgccctcgccctcccaccagaactctgctcctggctacaggc 300
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
ID 6: 56393 cccttgaggtgggagcctcgccctcgccctcccaccagaactctgctcctggctacaggc 56334

ID 5: 301    cccagcaccacccagttccgagaggcgtaggtcatcatgtgggatgccccctcccccctc 360
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
ID 6: 56333 cccagcaccacccagttccgagaggcgtaggtcatcatgtgggatgccccctcccccctc 56274

ID 5: 361    tgagtccttttcttgattcctccag0gtccggttgctgggtgtggtatcccaaggccagcc 420
             |||||||||||||||||||||||| ||||||||||||||||||||||||||||||||||
ID 6: 56273 tgagtccttttcttgattcctccag0gtccggttgctgggtgtggtatcccaaggccagcc 56214

ID 5: 421    caccctggtcatcatggaactaatgacacgcggtgatctcaaaagttatctccggtctct 480
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
ID 6: 56213 caccctggtcatcatggaactaatgacacgcggtgatctcaaaagttatctccggtctct 56154

ID 5: 481    gaggcc 486
             ||||||
ID 6: 56153 gaggcc 56148
```

FIGURE 5

```
   1 gaattccaga tggaagctga cttcctgctc agccctatta aaaaaaaaca caggctttcc
  61 tgcctctgag ccccttcgcc acaaataact tgagtgccat gcacggaggt gcccacttgt
 121 ggcttaggtt ctctcagacc ttgtttgtcc ttcagccccc tggggaggag cccaggctac
 181 cacctgctgt ccctaagcct aggacccagt ggagaccatc gaattgcaga tttagacaga
 241 attaaccatc acagggcctc ataccatcct ttttaaagga ccaggccttg atggagactg
 301 cagtcgccaa cccccatggt gcttttgcta ctatggaaac actgaaataa ccaacacaca
 361 cactggttgt ggatgccact gaacacacac acacacacac acacacacac acacacacac
 421 tggttgatgc ctctgaaccc caaaaggtca gcctggaagg aatggtggct gctctgtcct
 481 ccatctcagc cgcacatctg aagtcacccc agccacaggc acctgtcatt gtcacagctg
 541 gtccctatgg gcttactctt tcctcacgat gctcttattt ttagtcagac accaaagcgc
 601 tttatttatt tttagttaga cacatttggc acatttcaag ttttccaact tgtattcgat
 661 aaagggaaac aaaggattcc tgtcacctgt cctaattgaa agcttctttg ataaatactt
 721 tcggacagtg attcatacta tcagccttcc aaaaggagga aggaaaaaaa aaaaaaagaa
 781 aagaaaagag cattcttttg agacactctt attcccttgc acttctgatt tgttttttt
 841 ttttttttt ttatttcggg tccagagatg gaatggctca aattacattt gacgtcctca
 901 ggaaaccata ctcttggtaa aagcagtgcc tgtctcaaat gaaatatggg catggaaatg
 961 tgctgccccc tcttggactc acgtctttcc ctacatttct ctcatcagcc agcagttgct
1021 gggagtcagg cgccattggg aaatgcccac tggatcccag agtgtggcct gcctttatta
1081 gtaatgtttt gagtttgccg gaggacagac tcttcatttt attggagccc ctagttgtgt
1141 aaatcttgtc ttgacaactg gtatgtagac agatggtgaa atgcaaggat tctaacaaac
1201 agcctttaga ttaaggtgtt ggctgggacc aacagtaaaa tgagagacca ggcgaacctg
1261 cagtcctccc cagggttcga tgattctacc acattttctg gctgactacc caactctatt
1321 ccaaggcagt cttgatgggg aatgaggctt agcccagcaa aacaagacct tctaaccttg
1381 ctcccggagt tgtctttcct aatttaaaac aaacaaggat gtagtttcct caaagctgaa
1441 tgtggttcta aagtgtgtga aatgtgtgtt gatgggtttt taatgatcct agaggaagct
1501 ggcttctcgg tctttctact taatctcaac attttctaag ccgttcttta gagctgcagg
1561 ttcccacagc agctgcaaga ctgtgtatcc tatcagtcaa agccagatgg tagtcctgag
1621 atggtgggcc attctgttga aaagctttct gtcccctgaa gtttttctcc ctaggaacca
1681 atcctgatga tgggccacga ccaatacact cagcagttgc caggcacagc tggatccctt
1741 ctccagtgct gctacctact ctagaggccc tggggtccag cgacttgatg tagcatcctg
1801 atcttttaca gactggaaag tgtggcaact gagaagtatg cgctgagagt caggtgaggg
1861 actcaaaccc tcagtcatac tccagataaa actgatcagg acgatgctca accctacctg
1921 cagcccaagc tgagatgagg ctccccctcct ctcagtctga catgctagcc tcccccagga
1981 ggaggccaca catttttcat tttagaaata tagatcaaga agaaattgta aagaaagaga
2041 actccttgca aatctcacta gggttgcctg atgctgacat cttcaatgtc caatccaatg
2101 tactaacatc agtacaatta agaaagagag aagcagagag agggggagaa ggaagggaag
2161 gagaacggga tggaggggtt gaggaatgag tatgtgtgca cgtgcacaca gaccgctcta
2221 tacaatttag accagtgcaa ggcttcctgg aattgcctcc acctcaaaac gccttccccct
2281 gctactccca ccttagcttc ttccgcactt tcttccccca ttttaacacg tggtgtcctt
2341 ttcagactca tttggctgta ataaaatatc cagaaaacaa acaaacgaca aaggataaag
2401 gagtttattt ccgtttacaa ttccaggtta cagtccatcg tggtgggaaa gtcagcagca
```

FIGURE 6A

```
2461 ggaacttcag agaattggtc gcatcacatc cacagtcaag agcagagaga aatgcataca
2521 tatttgctgt cttgtttgct ttctcatgtt cagcttggat ttctccattc ttttatagtt
2581 caggactcaa tgcctaggga atgacactgc ccatagtgaa ctgggttccc ccacatcaat
2641 taacaagaat tgttgaggaa ttgggttggc ttgtggacat ggtttttttt tggaggatta
2701 tcttagttaa gctaattgat ataagcagaa ccattcccta ggcaatgatt ggcctgtggg
2761 catgtcaaca tttcctagga atgttggcct gtgagtatgt ctgtgcccac aagtaagaca
2821 attggctaat tgatatgaga aggcccagcc cactgtaggt ggtaccattc cttaggctgg
2881 agatccttga gctgtaggag agaggagaaa tcaaactgag cacaagcaag tgagcatgtg
2941 tgcatctctc tgctctttga ctgtggatgc tatgtgactg ttgtttgaag tcctgcctca
3001 actttcccac agtgatgggc tataacataa ttatatgctg aaatgaattc ctctctcctc
3061 taagttgctt tcgttgttgt ttttattaca gcaacagtta aagtagaaca cttatttaaa
3121 acctatggaa ggatatatag atagtttaca gctttagagt tgttagagtg gagaacacta
3181 ctgtaaacag tagtttccag ttctgagatc agtggccagg tgtatacatg ttactcagtc
3241 cactttcagc tctaaaaaaa aaaaaaattg gggctcagcg gttaagagca ctgactgctc
3301 ttccaaaggt cctgagttca aatcccagca accacacggt ggctcacaac cacccataac
3361 ataacaaggt ctgatgccct cttctggagc ttctgaagac agctacagtg tactcacata
3421 taataataat aaataaatct ttttttaaa tctatcacca tattgcaaag tagtgtcttc
3481 cattcctatc aatatgtgag acccagtttc tcattctttc tttgtttgtt tgtttaagat
3541 tttatttatt cattgtatgt atatgagtac actgtagttg tacagatggt tgtgggccat
3601 catgtcattg ctgggaatta aattcagtac ctccgctggc tccggccccg ctggctccag
3661 cccaaagatt tatttattgt tagacctttt aaatatatca cataatagtc tttatacaat
3721 agataagtgc tttctcagta ataacctctt aacagagttt ttatttttta tttttaacag
3781 agtttttaaa agagccaaca ttcttaactc tgtggctgta tttttgcttg tcttgtttta
3841 aaacaagctc ttgggtggtg gtagtgcaca cctttagtcc cagcagatac tggcagatcc
3901 ctatgaactg gtcgagagag caagttacag aaaagtcaag gttacacaga gaaaccctgc
3961 taactaaggt tgagatctgc tatgtctaga tggcttatct gagctcagtg caaaatggag
4021 gactctatac catctgggct tccccttctc tgaccttgtc taggggactc cctatactct
4081 ctacctggga aaggtcaagt agcctcggaa gaccaacaaa cttcctcttt tccgcagaag
4141 aacccaccca acaagtaccc gggattcctg aaatgcctct ccatacaaat gaggaattcc
4201 aagaacttta aactctaacc aatgattttc atttaccctg aaaactcctt cacactctcc
4261 aaggtcctgg tttaccccaa ataaagtgta ttcgtacaag ccccacccta gtagaggtat
4321 ggaggtatgc tcacaaacca agatcggcta agagagctgt tttcattgaa gattgttgga
4381 gaaggccttc ttctaaaaga gctgtaactc taagatcctt cgggaaggcc ttctctccct
4441 tccctccccc tccccccact agcactcact cccagcagga ccctaatcct gtataaccct
4501 ccccccccc ccattctgga cactgtttca tccttcccac ccagtgtgca gtggcatctg
4561 gatacctccc tgactatgtt tcatacagtc aattctgagg aagcccccag attagcaagg
4621 ctgaggttct ctggggccta tagaacttgt tgccaggtga tagaacttgt tactgggtag
4681 tgtgggctgg tttgagcaaa cctgggtatc tttggtttca ggttttgggc ccttccggca
4741 gcacctagtg aattccagct gggaagccgt gaaggtaaat cctgccgttt gccccccccc
4801 ccccccccc ccgggccaac ctggttcctt ctgtggctct tgggaaaccc caatgccaat
4861 gcgcgggact cctaagaaac cagagtcacc ttggaaggaa ggcaagcagt gggcccctgg
```

FIGURE 6B

```
4921 aagaaaggct tgtatttggt cctggaatgg tgtgacttgc ctggtcaggt acttctctcg
4981 tttgtccagg gacactccta ggtgggacca aggcccatgt aggctctact ctacgtaggg
5041 ctagattctt gccctctctt cctttggatg tggggtctgg ggaaagtcat tttcaccagc
5101 tcttgtcctc acctacgcat gcggaagtga taacatggat gtctctggcc tccactgaca
5161 gctcagggtg agggcagcct tgtccacact gctctgtgtg agcccagcat ggggcgtggg
5221 tgagaacctg gccagtgctc gtgactgtcg acagcacgct tgcttttgag gacatagcta
5281 accaggagaa gggaagtcct ctgaccgccc actgtgcata ggagggcagg actccctggc
5341 ccacccccac ctccctaggt caactgtctg ccatcagtcc tcatgtgggt gtcacttaga
5401 ggctctgcga attgaaagct gcctgttcgc acttggcttt caacttcaca ctgatgttgg
5461 accaagccaa atgtggggcc tggagtctat tctcagagtt tcccaggcca gctgagaaac
5521 gcagcaaagc tgctagcgtc atgcactcac agccaccgtg gcactgactt tgtggtctga
5581 caacgcagag gcaggcagga gactcttgat ccttgagtta gcatttgggc ttttgctttt
5641 ccaatcataa aaaagcccag agacccttgg actcattgcc aagccttgct ctggtacaca
5701 aggtaacaga gaggccagga ccagactttc atgagctcct ggctttctgc aaccagtatt
5761 tgatcagcag gacttctgcc aagtcctcag tagtcccaga ccctttttgtt tctttctgca
5821 gccgtaaaca atggaaaaga gccagactgc ttctggtttc tggtttgcct ctcagtttcc
5881 ccagttgcaa gtagtggcat tcaaaaacct tgctcgagtt ttgatgcctc cgtttcccaa
5941 tttaaataaa tgtgtgtgtg tgtgtgtgtg tgtgtgtgta tgtgagagag agagagagag
6001 agttgaggaa gtcacatgac atcccaaaga cctcttgggc atgctgatag agctcacagg
6061 ttgtccattc ccaccaggag gcttttctgt ttgtctggta cacagctgca gacacatggg
6121 atgagggtca gatcagcaca ggaagtggca gaagggagag ggttacctga ggtggttggg
6181 aaaccccagt gcttgggact gctagtaatc aaagtcacct tggagggaag gcaagccagt
6241 gaccactgga agaaaagttt gtctttggtc cttgggtggt gtgacttgac tggtcaggta
6301 cgtcttccat gtgtgcagta aagaaaagtg gctaaggagg ctcaaggctc attaagcttg
6361 gtgaagcaaa ccagacagac acagggactg gggcttgcct gaaggcatat agtcagacat
6421 gcagacagcc aaggatagct ctgaaaagtg cacacacata cacactcaca tgcactatac
6481 acacacacac acatacacta ttcctacaca catataccac aaacactata cacataccac
6541 acacatacac tcacacacac tatacacaca ccacacacat atactcacat atactataca
6601 cacacacaca tgcactacac acacatatat acacacatac actctcactc aggagctata
6661 ggctgaggaa agcaagcata cactggaatg gcaggtaagg acaaaatctg tgttaagggc
6721 tggaggtatg gcttagttag tagagaactt ggttgcatgc atgtgggtct gggtaacatc
6781 ccagcactac ataaaatcag gcatggtgtt atacctagta ctagggaagt agaggcagta
6841 gaattggaac ttcaaggcta tgctctgact gctgcagact ctcatggagt ttttgtgaga
6901 atttaaaatt caaattctgg gtttggcatg gtgacccatg cctttaatcc cagccagcat
6961 tcaggaggta gaggcaggca gattactgtg ggtttaaggc tagcctggtc tgtacagtga
7021 gttccaagac aggaatatat agagagagac cctgtttcag aacaaacaaa aataaaactc
7081 aaacttctta caaagaaatg tgaactatca gttcctagcc taagatcacc tgatacacaa
7141 gaaaataaaa taccatgtta aaaaaaatca gtagatgccg ttttaaaaaa cagaattata
7201 accaggcagt ggtggcacat gcctttaata aacccagcac ttgggaggca gaggcaggca
7261 gatttttgag tttgaggcca gcctggttta caaagtgagt tccaggacag ccagggctac
7321 acagagaaac cttgtctcaa aaaatcaaaa aaaaaaaaaa aaaaaagata gcagtctgag
```

FIGURE 6C

```
7381 aaattagaac tatagctgac ttaaaagaca gcttagatct gtggtcagtg aaagatactg
7441 ctcacaagag actgtatcac ttgagtccac ttgcattaat gtccctagta agtaaatata
7501 ttgagagagg aagtaggtta gtgataggct aaggtggaag gacacagtaa atgaatgtga
7561 agtttcctta aagtacattt atttatttgt gtgaccatgt gtgtgtgtgt ctgtctgtct
7621 gtgcacacca tggcttgccc atgaaggtca aaggacaaca ggtaggaagg agctagaact
7681 ctccttcccc tgtataggac ctagggatgg agctcacccc agacatcggg tttgggcatc
7741 aggaaccttt accccgagcc tctcacatac ttctttagga ttctttaggt tgtaattcaa
7801 aggctctggc accgattgcg gtgatggttg gttgtataac tcttgatggt gatggttata
7861 taactgagca tactgaaaga tgtggagtta aatagggtaa gtacgtggaa tgtgaataag
7921 ctatctctta ggagatagat gataggaaga taggatagat agatagatag atagatagat
7981 agatagatag atgtgattag atagatagat agatagatag atagatagat agatagatag
8041 agataggtga tagactttac ccacatgtac acatatatag ctgttcagaa acagacgaag
8101 agaaattagt aaactagaat atagatatgg agatattatt caaaggacaa tataaagatg
8161 ggcaaacaag catagagggg ataatgtaaa tagtaaagga agtttctgtt taaatagaat
8221 tccagaggaa aataacagcg agaatggaag aaaaccatct tcaaatatac agctacaatg
8281 tatgggattg gaataggttt ggtcccatag actcctgtgt ttgaatgctt ggcccacaag
8341 aagtggcact gttaggaggt gtggccttgt tggatgtttg accttggtgg aggaagtata
8401 acactgtagg ggcagacttt gaagtctcct atgctcacgc tatgcccatt gtggcacacg
8461 gtctcctttc tgttgcctgt ggatcaagat gtagaactct tgggctggtg agatggctca
8521 gtgggtaaga gcacccgact gctcttccga aggtctggag ttcaaatccc agcaaccaca
8581 tggtggctca caaccacccg taatgagttc tgatgccctc ttctggtgtg tctgaagaca
8641 gctacagtga acttacatat aataaataaa taaataaata aataaataaa taataaatct
8701 ttaaaaaaaa aaagatgtag aactctcagc tccttctcca gtgctatgtc tgcctggatg
8761 ttgccttgct tcctgctctg acaataatgg agtaaacctt tgaaattgta agccagcccc
8821 caattaaatg ttttccttta taaaagttga cttggtcatg gtgtctcttc atagcaatgg
8881 aaaccctaac aaaggcacaa tggttaagaa tattccagag ggactggaga gagatggctc
8941 agtggttaag agcactgttc ttccagaggt cctggagttc aatccccagc aaccacatag
9001 tggctcacaa acatttgtaa tgggatctga tgccctcttc tggtgtgtct aaagactgta
9061 ctcacattca taaaataaat aaatctttaa aaaaatttcc agaactgatg aaatacttga
9121 atccacagag atagaaataa agaaaatcca cacctaaaca tagtagagtt ggagactgca
9181 aaagactgat taaggcttta gagtagccag agaggagatg gcttacttac aaaaatggat
9241 actctaacta gtagtctagg gctaactttc tcaaaaatag caatacaagc tcaaaagcag
9301 tacagtaata acctacagaa tgccaaaatt gtagctgctg aacagaaacc gtgtagctag
9361 gagatcattc ctcgagaata aggctggggc tggagagatg gcttcgtggt taggagccct
9421 tagcggttat gctcttcctg aggacctgcg tcaattccca gcgcccacgt caggtagttt
9481 ccaactgcct ttgatcccag ctccaaagtg aacctctaac ctttgggagc acttgcgttc
9541 acgcaagtga acacatacct ccctatacac atacacataa ttaaaataaa aaataaatct
9601 ttttttttt ttttaaagaa taaggctgga gtaaaaacat tttcacaaaa ataaatgtca
9661 ggtttactct cagaaggatg acacaagggg actgtaaaaa ggacacttgt cagaagagaa
9721 gaaaattatc acaaaaatgg tgtcttagtc agggttttat tgctgtgaag agacactgtg
```

FIGURE 6D

```
 9781 aacacagaat tgggggtggc ttatagtttc aggggttcag tccattattg tcatgacaag
 9841 aaacatggag gtaggcaggc agacaaagga caggagaagg agctgcgagt tctacatctt
 9901 gatccacagg cagccatagg agactatatg ctatactgtg catacctcaa gcataagaga
 9961 cctcaaagtc actatgggga atgcttgccc catagtgact caatttctcc aacaaagcca
10021 tacctatcca acaaggccac acctcttaat atagtgctga atagtgctgc tccctatgga
10081 ccaagcattc aaacacagga gtctagagtc ttatgagggc cattcctatt ccaaccactg
10141 cagatggtat agaaatcact gggaagcctg gcagtggtga cgcatgcctt taatcccagc
10201 acttgggagg cagaggcagg tggatctctg agtttgaggc cagcctggtc tacagagtga
10261 gttccaggac agccagggct atacagagaa accctgtctc aaaaaacaaa aaaacaaaaa
10321 caaaaaaaca aaaaaacaaa caaaaagaaa gggagggagg gatgaaggga gagagagaga
10381 gagagagaga gagagagaga gagagagaga gaaagaaatc actgggaaat ggtgagtctg
10441 agggtagaaa tctgtaccag caccaggcag tgatggcaca cacttttaat cccagtactc
10501 aagatctggt ggatgtctga gttaaaggcc agccttatgt acagagtgag ttccagatca
10561 accaaggcta catagaaaaa ccctgtcttg aacatcaaaa caataaacaa acataaagtc
10621 catatcagca ttgtttgtaa catgtaatag tagtagttcg taattccagg atggaactaa
10681 aattcacaac agtcaaaggg tcggtggtct tctccctcca gtgcccctca ttgtcggtga
10741 acttcaagct catctccacc atctcttcag tgacaggttc tggagcaggc tctgctcaat
10801 cttcttgctt ttaataggac caaaggatgg tgactagaca cacctgcatc ggcacctgga
10861 aagtgaggtt cccgagatgg ctggctatgc ccaggctctt ggtaccccag ttggccttcc
10921 ttttggcccc tggactctag gtcttgcatc tattctccct tccttgtgtt cttcctttgg
10981 acagagttgg ttgcaaactc tttgctgtca atgtgcaggg ttgttttgtc cccacgggtc
11041 aacttaggtt atcctgtgtc ctgtctaaca cctcagtgga ctctattttt ggttcagcat
11101 cttcctattt ggttttcagt agtcactgaa agtgctggca aacagttaac agtgtcttta
11161 gtaggaatgg ttatctaagg gaccatacta ggtaaagggc tgagatactt catatacata
11221 gcataccctg actgctgtaa agatagaaaa acagactgag atgccctaca cagtctgtgt
11281 ctgtataagc tacacacttt ctgtaatggc caacatcaat ttatctttat cccatagagg
11341 gcctggcttg gagcatgtgt tccagggact gaatcatttg aggtaggagt gaatactttt
11401 ctttctatcc tcttgcattc ttccagtaaa attaaagctt atcgctatca tgtatgttcc
11461 caagcaatgt ttaattatct gtaaaaagct ttgtatctga gactgcatgg attacagatg
11521 ggaaaggaaa aaaaagtgtt tatttccaca gtgtctcact tccaagaatg gggtgagcta
11581 ttgacaaacc atcacacgaa gacatttttt tttaaagatt tatttattta ttatatgtaa
11641 gtacactgta gttgtcttca gatacaccag aatagggcat cagatctcat tacgggtggt
11701 tgtgagccac catgtggttg ctgggatttg aacttcggac cttcggaaga gcagtcgggt
11761 gctcttaccc actgagccat ctcaccagcc ccgacattat ttttttgtt gcagccactc
11821 ataaatggga gaagaatgtt gaaaggaaaa gaaaatgtag gggctggaga gatggctcca
11881 tggttaatag cactgactgc tcttaccgag gtcctgagtt caattcccag caaccacatg
11941 gtggttcaca accatctgtt acaggatctg atgccctcct ctggtgtgtc tgaacacagc
12001 aagtgtgtgc tcacataaaa taaataaatc ttaaaataga aaaaagaaaa gaaaatgcag
12061 aaaaataata tgaagtctaa aagttcacag cgaaagaggc attttctgca aagttcccaa
```

FIGURE 6E

```
12121 gcaagtgact ccatgctgtt tgttgatcag cattgtgagc cctcgtgttt aacattgagc
12181 taccccatac tccacaagcc caacgctcct tcagtgacat atgcagcagc tgcatcatca
12241 ttgcccatga tctagattct aagctctagg tgtggtggtt tgaataagga tggctcccat
12301 agactcatgc cagggaatgg cattaggagc tgtggcctcg tgggaggaag tatgtcactg
12361 agggtgggct aataatatag aagttagtac caaggactgg ggtttttgct gccctaggct
12421 ggaccaagtt tcttggtgga atgtggactt tggattagga aaatagttga atggttcaag
12481 tagagcatca caggccatac tggtaagacc atggaagatg gtgctgttgg tgacatgaat
12541 tatggggtac acaggtttta gaggagaaga attgtaggcc tagatttttc aaaccctact
12601 tttaataagg gttcttaaac gctttatcct ctcttctagc ccaccaccca ccagagggag
12661 tggaaaggaa aggttaatag agcaaaggag ggtgtggatc tgtttagaaa aagttctttg
12721 gagcaaatcc aatctgtgtt accaggatat cagcagtaca gttcactcag aacagcagca
12781 gcagctcgat ccacttgcaa acaccattca tgaatcagca atggcaggtc aatccagaag
12841 aaacctcgag gctctgccaa gtacaaggaa gcagcagcaa gaagctgcca gaaagaacac
12901 caccagaagt tcttttgtgg catttctgtc tatgaagtca tatcaaatga tgactagcaa
12961 agaatggcaa ggcaaggtgc tggtgagatg gcttagcagg taagagcact gactgctctt
13021 cccaaggtac tgagttcaaa tcccagcaac cacatggtgg cttacaacca tcgtaatgag
13081 atctgatgcc ctcttctggt gtgtctcaag tcaactacag tgtacttatg tataataata
13141 ataaataaat taaaaaaaaa aagaatggca aaccaaacca tacagcttca tcagcgaaga
13201 ccagtgtcag caaaacccaa tgataaccag caaatatata tatcctttcc aaacatcaca
13261 ttcttgttct ctcaagtgtc agctttagca aaacatcaca tgccctttgc ctagactgct
13321 tctagaaaac caccgtgtat ctgttctcag caaaacatcc tcccacatgt ctgcttcagc
13381 aaaaacatcc tctcataaga cagtttccag aaaaacatca catgacatga ctgcatctcc
13441 aaagaagcca gaaatttcca attcaaagag tactagtatg caacctagag accattcttg
13501 tgatattttg acaaagatca tgggtacatt ctgctcttgt catgcacaca gacacacaaa
13561 tctgcctgag gttaaataga agagttatga atgaacatct ttagaagatt tgtctctaag
13621 agatttccaa aaagtttagt attgactttg ttgcttggtt attagtgacc atacttatgc
13681 agatctgtaa cgaagaggac caagctaaac aaggaacata cagaatgtac agtttgagga
13741 gaaaaggagc ccagggaagt gtaatggagt caagtccagt gcttgaggag ataaacctga
13801 tgttaaatgg aaaggagaag tggtgacctc aagccaggac tccacctagc taagcttcca
13861 acttctgaga agtaatcaaa gaaaagttta gaactgggtg tagctgaatt accttgaatg
13921 ttagcagcac tcatgagaca gaggcagcag gcaggtcact gagttcaagg ccagcctggt
13981 gtacagatgg ggttccagga cagccaagct taggcagtga aggaaaccac tgaaaacaga
14041 aagctggtga agatggattt gaatgaagag gcacattcca ggcccagcag cagcagaact
14101 tggtagcttt ggccatattg ctctggcttt agagtggagg gtacaaaaaa aagagttatg
14161 gaatctccct ccgtgactaa ggaaagctga tggggccagg tgtgtgtcag ggatgtttct
14221 gcatggagac ccagagacct ttgcttaaag ttgtgcaggt aaaaacctgg attgttgtga
14281 tagtttgaat gcttggccac agggagtggc actattggga ggtgtggcct tattgaacga
14341 agcgtggcct tgttagagga agtgtgtcac tgtggaggca ggactttgaa gtcatatatg
14401 ctcaagctct gttcagtgtg acatacattc tccttctgat gcctccagat caatatgtaa
```

FIGURE 6F

```
14461 aactctcagc tcctccagca caatgtctcc ttggatgctg ccatccttcc cgccatgatg
14521 ataatggagt gaacctctga aactgtaagt cagccccaat taaatgttat gagttgccat
14581 ggtcatggtg tctattcaca gtgatggaaa acctaactca gacgattgcc ccagaaagcc
14641 cccaagatgt tggatatgcc agagtcatgg gatttgtgaa gagggatgct gttaacaggg
14701 agtggaactg gcccaagaga aataactgtg ttgcagtcaa caaagttgaa aagagttgga
14761 gatctgaaga ctgctttgac atcaggcacg gagatgcaga gtttggagtt tacacagctg
14821 ttttttggtc ttgcttttgt ccagtatttc ccctttcctc ccttttggga tggtgataga
14881 tatcctgtat atgttggaag tatgtgatct tgattttgat tttattccag atcatagtta
14941 agagcttgcc ataagtctta gaacagactt tggactttta agcagggtta agactgatag
15001 actatggaga cttttgaggt aggattgagt gcatttctgg attatgataa agctacaagt
15061 ctgtggggac tgggatgtag aatgtggtgg cttgaaaaag aatggccccc acagacacat
15121 acttgaatgt ttaaggggta tcattagaag gtgtggcctt gttggagtag gtgtggcttt
15181 attagaggaa gtatattatt gggtttgggg ggtggtgagc tttgggtttt gtctttgtgt
15241 atgcctgtat gaggaggtca gatcttttga gactggagtt acaggcaatt gtaagctgcc
15301 atatgggtac tgggaattga acccaggtcc tctggaaaag cagccagttc tcttaaccac
15361 tgagccatct cttcagtccc gttccaatga atttttgaga agcttttcta gaagtgcctg
15421 aacccagaga gacaataaaa acagttgttc tcaacctgtg agttgagaca cctttggggg
15481 ttgcatatca gatatttatt tacattgatt cacaacaatt gtaaaacttt cagttttgaa
15541 gtcgcaatga aataatttta tggttggggg tgtcattaca acatgaagaa ctgtattaaa
15601 gggtcacagc attaggcagg ttgagaatca ctgcaacaaa agaagaattt tgtgccaggt
15661 ggtagtgcca tgtgtcttta atcccagcac tcaggaggca gaggcaggca gatctctgag
15721 ttcgaggcca gcctggtctt tagagtgagt tccaggacag ccaaggctat acagagaaac
15781 cttgtctcaa aaacaaaaca aaacaaacaa acaaaaataa ggtatttgta aaacataccc
15841 tagatccgtt gtgctaagac ataacagcat tccaaatata catagcccaa gtagccaagg
15901 ggttagagct cttatcagct ttgatgagct tgatataagg ggaatttccc tttatcccca
15961 aagatgaagt ggtcttaacc ttcttgcatg ctgtttgctt gttagttaat aggtttattt
16021 ttattttatg tatgtgtgtg ttttgcctga atatatgctg tgtaccttaa gtgtacttag
16081 tacatgagga gtccagaaga gggcgccaca tcccacagaa ctggagttac agatggttgt
16141 gagctgctgt gtgggtgcta ggaatcaaac ctgggtcctc cagtgctctt aactgatgag
16201 ccatctctcc agccccttcc atgattcttt aaaaagcagt catagtgaag agagtacaag
16261 gttgtgcatc aggacagtaa caccccaat ccatttctgt aacaagtcag agtaagatga
16321 cagatctttc aaagggacac cagcaactgt ctgggccctt cctgtaggtc cccctaaact
16381 tcactttagt ctggagaaat tccagggctc tcagattact ccagagagct agaaagagaa
16441 gcttttcttg tctcgttttc cgtttgtgtt tataacataa acttttattt atttatttat
16501 ttatttattt atttatttat tatatgtaag tacactgtag ctgtcttcag acactccaga
16561 agagggagtc agatctcgtt acggatggtt gggagccacc atgtggttgc tgggatttga
16621 actcgggacc tttggaagag cagtcaggtg ctcttaccca ctgagccatc tcaccagccc
16681 tataacataa acttttaatt tcactgggaa gacattcaag cagaggtccc aagttctatc
16741 actcagaaca catatacaga tctggacata ttgacatgca catgaaatgc aatggagata
16801 gagagacaga aggatccctg gtacttgctg gccacccaga ctggtagaac cagcaggctc
```

FIGURE 6G

```
16861 caggtagctt cccaaccatt tctccatctt tgggtccatt gttgcctgtc tgaatatctt
16921 tgcagatagt ttttagaggg gaaatacagc aagtaagcag aatggtgcag ggtagagcct
16981 gcacctggaa agtggagaaa catcctagag agacacagcc ttgcaaggct ggtccagggt
17041 gtgggcagtg tacagctgtg actgcagatg tcagcacaga tgctgggtac ctgattcatg
17101 gcaaccacag gttgggaggg cccctacaga tgttggagcc ccaggtctga caatcccagt
17161 ggggtgattt gtgacgtttg taataagatc agatgtgagg gtagaggtga gagagagggc
17221 ccaggtagcc ttctagacct gtctttggaa tctgagttca gactggacat tttgggggct
17281 catttccaga gtcactctcc tgtgctctgc tcccatattc atgagaagag cactcccatg
17341 ctggcagaac atgaggccca ggaagaagac atggggctct ccataactca accccagaga
17401 cctagtgcca agcaattatt gctcatagca gccaaaaaca tgtaagaaac tgccccattc
17461 tggcgaaaga gtaagatgca tttgactgtg actgtcaccc attgtcagga ggccaaagca
17521 tttctttagc agctcctcga gtcaatgaaa tactgagtgt actgaggacg agggcagctg
17581 atgtcctttc tcatctgtgg tctcagtgaa cagaggtcaa ccaggatcca aaaagcagta
17641 ttatgtggaa actcccagaa agaaaccaga aaggagtttg atggtcacga gactggacac
17701 actgccagag tcgcgtggct agcgtcagca aaagttttca agtgacttcc acggaagcat
17761 atttacgacg acgtacagaa gaagggcagc tacttaacag atgcccacct acctttaga
17821 acagctaata agtcacagat gcctgcggta ctcccagaac agaggggcct tagtagtcag
17881 gcctcacaca ggaggcagga agaaaagcat gcaggaatca aaccatagcc taaagtataa
17941 gatgaacatc caggagccta aaccactcta aagaaaatta catagatcct ctatgtaaat
18001 taaggagcag gagagtgagc tttaagttgt ttctgcaggt gcataaatta tgcaggcact
18061 tcaggcccta tggagaactt aaccctcctc ctcagatgct ggctgcacgc ggacttcctg
18121 ccacaggacc cctgctatga agtgagtgca ggaaagaacg ttttatagtg aagatgcctg
18181 agagacttcc aggccaggtg atccaagtca acacctacag tgacaagtct tgttgatggt
18241 ttgtaccctt gaaatattat catgagaagg gcactctatg cctctagagt cttctgcccc
18301 caaccctaaa gcccagtctg atctgagacg agaaggagac agattccagg gaaggcacac
18361 gctctacagt gtctggccag tgttccatag aaccggcaaa gtcattaaac acaagaaaga
18421 actgtaggag atggaacaat gtgttgtgat gacctagatg gaccttaaag gactgctctg
18481 tgtgtgtgtg taactaagga acctgggtaa acgatgcggt ccttaccact cttctatcca
18541 ttaaaatgtt tatcatgtct cttcgtggtg gtgcacgcct tttaatccca gcactcagga
18601 agcagagaca agaggatctc tgagtttgag gccagcctgg tctctagagt tcagggctac
18661 acagaaagac cctgccttga aaccaaccaa ccaaccaacc aaccaatgaa ccacccataa
18721 cccacagatt tttgttgggt gtgcttttgt tggaacctcc ctctcttttc tcagttttaa
18781 gactccagaa ccgaagtgag aacagctggg catgttactg tgtgcttggg atcccagcaa
18841 tggggaagag gagacaagac tttcctggca cttattggta agctagccta acttacccta
18901 ggtgagctcc gggccagtga gagactctgt attaaaaaaa aaaaaagtgg atgttaaaag
18961 acacctaagg ttgtcctctg gcctccacat gcatgtacag acatatgcac acatgtgtgt
19021 gcacacatga ctgtttcctc ttgtttatca cctgtcctta tgatttgaga gaactgtagt
19081 aggctttcag atacagaagt ggattggctt ggttaaaaat cttagttcca ctactggcct
19141 gtgtaaaaga tggggaatct ctgctgagct aagccatgca ctatgagaac agtctctctc
19201 caggccagac ctctacaaaa aaaatcccaa caacaacaac aacaacacca ccaccaacaa
```

FIGURE 6H

```
19261 cacctttgca ggaaggtgtt ggtaaaggcc ctagtttaaa aatggtgtta catatacaca
19321 ccatgaagtt cagagagtcc attcgcaaca ttatttgacc ttcagcacga tttgtttctg
19381 gaactttccc accccattct tgcctcgttc ccccaggtcc tggtgactgt tattattttg
19441 tatccatact gttgcacagc aagtgtctag aactttctga atctgcagaa cagactcgct
19501 actgatttaa ccatggcctc ccctcccccа cccttccccт ccccttggct tctgctgacc
19561 accactctac ttcccatctc tccctcgttg gctgttagct acttagtgga agtggaacca
19621 tattgacttt tgtgactggc ttacttggct tagtataatg ttttcaaggt tcaaccatgt
19681 cattgagtgc accagtacat tcctaaaacc ctggcactca ggaggctaag gtaggggaac
19741 ccagaccaat ggttttcaac cttcctcgtg ttgcggtgac ccccacaacc atatttctgt
19801 tcttacttca tagcagtaat tttgctaatg ctatggatca tagtacaaat atttttggag
19861 atagaggttt gccaaagggg gtctcaatcc acaggttaag aacttctgat ttagactttt
19921 agttcaggcc aaattacaca gtgagagcct atctctttca tttcctaatt tgaaagaaag
19981 aaagagggag ggagggaggg agggaggggg ggggaaggga gggagggaag ggagggaggg
20041 aagggaggga gggaagggag ggagggaagg gagagagaga gagagaaaga gagagagaga
20101 gaaagaaaga gagaaagaaa gggagaaaga gagaaaaggc taggcgtgat gcagctcact
20161 gcagctctgt gagacgcagg caggtccatg gtcttcccac ttcagccgcc tagtgaattt
20221 gaggccagcc tgagagataa gagaccctgc ctttaaaaaa caaaatagac aatcagctta
20281 gtgggtaaaa gtgtttgtga ccaaagctgc caacctgtgc tggatcccca gaacccacat
20341 ggtggaagga gaaaaccagt tcctgcaagc cctccacgtt gtgagccatg gcatgcaggc
20401 atcctcagac agacagacag acagacaaaa tgaataagta cattaacatg tttaaattaa
20461 aaaatggaag gggcagaaag gggaaggaag cagatggggt cttttgtttc tttgttttgt
20521 gtgtgtgtat ttatgtatat atgtgtgtat atgtatgtat gtatgcatgt atatatgtat
20581 gtattagaga caaggtttct ctgtgtagct ctgactgtcc tgaaacttgc tctagggatg
20641 aaatgcatgc acccccctcc cccagctgaa actgacagtc tgattcccta ttgtgcttgt
20701 gtttcttacc agttcatcct ctgctggaca cttggatggc atcttctatg ccactgtgaa
20761 cagagctgca agctttcatt ttgggggtat atactcagaa gtgggggtac tgggtcatat
20821 gaccagtcag agattgttta gtaactacca agttctctac atatttagaa atactatttc
20881 ttcttctttc ttctttcttc tttcttcttt cttccttctt cttcttcctc ctcctcctcc
20941 tcctccttct tccttccttc cttccttctt tccttccttc ctttcttttct ttctttcttt
21001 tcttttcttt ctttcttttct ttctttcttt ctttcttttct ttctccttcc tttctccctt
21061 ctctcttctt cttcttcctt ccttccttcc ttccttcttt cttcttcttc cttccttcct
21121 cctcctcctt cttctttctt tctctcttct tcttcttctt cttcttcttc ttcttcttct
21181 tcttcttctt cttcttcttc ttcttcttct tcttcttctt cttcttcttc ttcttcttct
21241 ttctcctcct cctcctcctc ctcctcctcc tcctccttct tttaagcttt atgtgtacag
21301 gtgttttgtc tacatgtata tcttgcacac cagaaaaagg cactggattc catgggacta
21361 cagttacaga cttgggaggc atgggggtgc tggtctttga actcaggtcc tctggaagaa
21421 cagtgctctt aaccactgag ttaactctct ggctccaata tttcatctct ctctctctct
21481 ctctctctct ctctctctct ctctctctcc ctctccctcc ctccctccct tcctctctcc
21541 cttcctctct ttctttttta ttttttattt ttctacttat tttcaatagc agccacctcc
```

FIGURE 6I

```
21601 acagatacaa agttctctga ataggccata aaaatctgag cttactcttg agtaatatgt
21661 ggtgaatgga cggcagagca tggccttctg tcttgcttgg tcctcacaca ggacacaggt
21721 cctcagacag gcccaggacc ctagagctcc tttgggggag gggacacagt ggtgctatga
21781 aagcctgtct tcttctactt actctcagtt cattataaag catttcaacc tgttaatggg
21841 ttccagggtc atactattct gccttaatta aactaatccc cacattatga tcaagaaatc
21901 ccataaaaat gatctgtaac aacatcacac ataggagata aaatgaatta atgtgaatca
21961 cacggaaatg aggaatgaca attcctgtga ccctcccaga ggcccttatc aaccatagga
22021 aaaaaaaaag agctgacatg ttgatccaaa tagaggaaag aattaggaaa agcagttaag
22081 gaaagaaaga ggcccttaca gatttacatc tgcccgataa agcccactcc aaagcaggag
22141 tcttgcatga gtgccatgta ccctaactac agagcagcag gggagagatg ctgaagtgtg
22201 cactgtgccc tgtgtcatcc agtcagtggt caggcatgcc acgtcaaaca tttttattaa
22261 cggggcacat gatcagaaat atttggagac agtgactgga tagagagtcc ctgtcattca
22321 tcctggatct tccaggcaag actgacacat cagtttggaa gaatcacata acagatactg
22381 gaagagggcg ctggcaagca gcctatgtgg aggatagaac ttgacagcac tcaggcagag
22441 tcacctttaa ccaacacctc aggatttctt cccaagctcc cctctgtatc tcttttgacg
22501 ctgcttcctg aaatgtcttc cctctaattg tgtccctgtg gactttggct gtcccctgtg
22561 taggatgggt ttggtatcga ctgttctcga ggctgcgggg aggagatact tagcagagtg
22621 ccaagagtcc tccaggggca gcctcggatg atgaccggac tattcattaa ctcagaaaaa
22681 aatggtgcct ggaagcatct taccaagtgt agttgttctg cgctcagggt atgctcgggg
22741 tatgtagttg ttctgctggt atgcttccct tctcagagga gttcagttct catggtcttt
22801 gtaacgtcag tgttacattg ttttaatggc tacatcattg ccaccaatgg ctagcctctc
22861 ctctgtctac cagccctttc ctttctcttc ttcagtgctg ggctggaacc caagactttg
22921 ctcatgctag actaggcaag ctactcagcc ccagccttgt tcatggcact gagtgcttcc
22981 atatgcccgg tgagctctcc caggtctggc tttcattgct ctcttcacaa gcctggatgg
23041 tgttggatac ctgatggccc ccgggtctct tctctccctt cagggcaagg ggaacatgtg
23101 atctctctct ctctctctct ctctctctct ctctctctct ctctccctct ccctctccct
23161 ctccctctcc ctctccctct ccctctctca ttgttactcc tgcttgtgga gccaagcaaa
23221 gaaaatgacc actgaacagt gaccacgtga caagttgggg aaagataagt agaaaagggg
23281 gcgagaagag gggaagggaa ggagaggtaa gaactatgca aagaaaggaa gaaaaggaag
23341 agaaagggga gggggagaga aaggaagcag ggaggaggac ctctgtacac ctccaaacta
23401 acccttcaag atccaaagag catcttcttc cctgtggccc tccagcggcc cggccttgct
23461 caactctcac agcaaccctg agcggagtgc ttgggtctgc attgcaccgg tggggaagcc
23521 gaggcctggg aggttccaac ctttgtctag aagcacctca tcctccgaga agatcagcac
23581 tgacagagag gtcacccacc tgcctctgag ggccacctcc ccagagccca gagaaggatc
23641 ttacctggga tctgtgggcg gccatctaac ccagaaggca tgggggtgcc tggaaatgcc
23701 aggaaaggaa gtcaggaaca gctcaggcag aaatgaaggc acaaaatggg ccccacattc
23761 ctggctgaac tgggatcaag agtgagcaca agcttctaag atctcaggct ttcttccttc
23821 caacctatct gctacttggc ctggaaggag gatgcccaca gccttccctg cctcacctag
23881 ccttccatca cctccttgcc cctctcctct cttcccttcc ttctgctttt cctttccccc
23941 caccccctcc ttttctttct cattcctccc ttctttcatt ttcctctacc cttccttctt
```

FIGURE 6J

```
24001 cctttcttgt ccccctccc aacaacaaca acaaatccat ggcttttgtt tctaaaatta
24061 tatccgcaca ataacctctc tgccaattcc aggcacacag agccaatgga ccagctccct
24121 ttggataatt caaattgacc ccaagatagc cctaccccac ttgtacctcc tccctttgtt
24181 taagaggttg ctctaagctc tttgtttcct gaccgaaatc cttccatggc ttcctattat
24241 cccagagaag tccacacctg actaagcatt ccacccagcg tctgcagcct tctcaagttt
24301 caatccccat ccttcctggg gtggagtgtc cctgttgtac ctttggtaga gatgactagg
24361 gactcatcag attacaccag gacagttgat gtttggatta gcagcagggg tgtgaggcta
24421 gatgcttatt tgccttgtgg catgcaggac acctgtcagc tgcggagaac ggctcgccat
24481 accaatttcc cgaagggcct cgggctcttg tgcttccttc tgctatgatg ctagcctcgg
24541 ctgctgccac gtgtgttccc agcctcctgc tctggcccat cttcatctgt ccacagacct
24601 cagtgttgca aacatggctt cttcagatat gtctccctag ggtgcccccg cttcaggaag
24661 tacggctgag agagccatgg ctctttggtt cctggtcact ttgagttcct ccataccagg
24721 agggatgggt tggagctcag agaagaccct gggcatacag tcttgggtgc ctttgtgtcc
24781 aggcaactaa ggcacctcac ccgctatatt ttgcaggaac tttctaagct gggcttaggg
24841 gtggacactg acatagaact tcgaactctg cagctgcctg tggattacag ggaggtaaaa
24901 cggaggctta ccacaatctg ggaagatttt caaccacaag taagtgatac ctggagaggc
24961 tgtgggtctg ggaacctgat gatgggccca gggcctagga actttctgga ccttgatcta
25021 gatttgaagg ctggagtaca cctgaattaa agcttctgtc gtgagattct gggtctgtgt
25081 ataagtttat gctgaaacac gaggtagata gtaaaagatg actgggggca agtgggccgg
25141 acaaaatggg aatctggtat taaagccagg aggactctag gatagctcac acctatccta
25201 aaaaaagaga ggccctggat taagccctgt gtatggctaa ttctggctgt tctgaggaat
25261 ttaaggtaaa gcgctttggg cctaggaagg tctgatgatg attcacccag ggttggtcca
25321 ccttcaaaac atcctgccag gggcctggtg tgatggctca cacttttaat cctggcacct
25381 gtgagtttaa ggccagcctg gtctagttta tgagttcaca gccccattcc aaactaacaa
25441 aagtaactac atagtaactg aatataagca ctgtgtaaac aggggcacaa tgccaggtgt
25501 ggtagctcac gcctttaatc ccagcacttg ggaggcagag gcaggtggat ttctgagttc
25561 aaggccagcc tggtctacag agtgagttcc aggatagcca ggactacaca gagaaaccct
25621 gtcttaaaaa acaaaaaaca aaaaaaccaa aaaaacaaaa caaaacaaaa aaaggacact
25681 gaccaaacac tgcagcaaaa tcctctgcaa ctgttttcaa aagaggacaa ataaagtcta
25741 ataagattcg attagactgt tgctagcttc ctttatgaaa gtttcattaa atacaggatc
25801 ctgttaaaag ccagcatctc ccagggtcat cttggatact tgctttcccc caactcctgg
25861 ggggaaagag agcacacaac ctcggatgag ccatttgaaa tacaaaagtc ctttttaatc
25921 cagaaaaaat ggggaaaagt ccttaaatgc agatgtagca tgcctaattc aacccaaaga
25981 tgtgttcctt ttgtatcagc accattactt aggggcctaa gcagggctcc tggaggactt
26041 ggagctagat ctgtttagcg gggctctgtc atcactggac ctctcttcac atctagtgat
26101 ctggtgtctg tcctgggatt tctgatatgt atgtccctac agcttgttgt gcatgtgggc
26161 atggactctt ctgccaaggc catctttctg gaacagtgtg gtaagaaccg aggctatcgg
26221 gattcagatg taagaggctt ccagccggag gatggagtgt gcctccccgg tggccccgaa
26281 gtgaggctgt ctgttgtcaa catgaaggag gtctgccggc gtgtggctgt tgagaatgtc
26341 gaagtggcct tttcccgaga tgcgggcagg tacttcagga ctccgtgtgc caagtgccaa
```

FIGURE 6K

```
26401 acagatggga gagagggatt atccttcaga gtcccttctc tctcctcaag aggctatcct
26461 atgttgtcca tgtggctgct ttggtcacag gcatcctatt tgtcacaggc actgcagatt
26521 aatttaacct cttctccaaa cgctgacagc ccctcccccc aagcaccttt cctctcttct
26581 agggataaag aaatacccga ggggagttgg cagtaaggga gtcattgtgg tgaaggtgtc
26641 ttaccactag ttgtttgaaa ggccggctca attctgtcat gaccgcttgc tggtcattag
26701 actctgagcc caagaaccaa tgtctgtctg gagtgttctt aggccatgtc ctttctctat
26761 cagaagagcc aaactcaagt ggtactaggc atgtgggcat ccataaactc atgcttcatg
26821 aaacctgtac ttactgtgtc tggcatcgac aagatctggg agtaatgggg agtttcatgt
26881 ggttgcaggt acatctgcga ttacacctac tacctgtctc tgcaccttgg gactgggcat
26941 gcggctctca tccatgtccc tcctctgtcg cactggctct cggccagcct tctgggcaaa
27001 gccttgcgag tcatcatcca agaaatgctg gaagaaatcg ggaaagtcca gactcaaagt
27061 acagcagctt aagggaagca gcaggggat gccttcctta gatgaaatgg agtgtttcag
27121 gcttggacgg agaagccagc tgtgctatga gaggctctaa aaaagggaaa cagttacaag
27181 gctgggggtg ggggtggggg tgggggtgtg gactcacaga atcacaatct tactttagtg
27241 tctaaagcaa gaagaaaatc cccaaaggcg gatgcttcat aaaggattaa ctaggggaag
27301 ttatgacctt tgtaactcca aagagccacc aaaacctagt gtcaagacca aatgaactga
27361 ataactctca agtgttcttt gaaaaagatt ttatttattt gtttgtttgt ttgtttgttt
27421 atttattata caatgttctc cctgcatgta tgcctgcatg ccagcccagg gcaccagatc
27481 tgattataaa tggttatgaa ccaccatgtg gttgctggga atcgaactca ggacctctta
27541 agctctcagt catcttccct gctttgtttt gttttatttt gagacagggt ttctctgtgt
27601 agccccgcct ggctgtcctg gaactcacag aaatctgccg gattctgcaa gaaaatgact
27661 ttacaagatt tcctttgcaa ataaaccaag gacattttac atatgacaga gccaagccac
27721 actaaggcag atcaaagccc aaggtggaag ccgggcgtgg tggcacacac ctttaatccc
27781 agcactcagg aggcagaggc aggcagattt ctgagttcca ggacagcctg gtctacaaag
27841 tgagtgccag gacagccagg gctacacaga gaaaccctgt ctcgaaaaaa acaaaaaaac
27901 aaacaaaaaa agcccaaggt ggactgggat ggcacaggcc accagcacag aacctagctg
27961 cttggctggt gccttggctg gagacccctc tctgtgagca aagagctcct gctccaaacc
28021 ttaggtccct ttgttccagg agtgggctct agtgacactt caggtcactt ggcacctggt
28081 cagacacatt aaaagaaaac gccgggcata cgcctttaaa cccagcactt gggaggcaga
28141 ggcaggtgga tttctgagct caaggccagg gctacacaga gaaactctgt ttcaaaaaac
28201 agaggcccag accccaaccc ccatgagcag ctcttccacc ccctctgcgc ctctccagtt
28261 tctcaagacc ctaagcgccc atttgcattg tatttttgt aaatagcttg gcatcccccg
28321 acaatacaca ctgcatcctg ttcagtcaca gctgatagtg ggtggtttgt atgcttgcga
28381 gccagtgtag aacactgttt ttttgctggt catttaatgg ttgggaggtc tgaagcatgg
28441 ctctgtgttc atctataaac ccgactaata aaaagtcctg gttctgacta cccagagaat
28501 gtgtcaccaa caacacacca gccaaaaaaa ggaaagaaaa aaaagaaaaa ggtgtagtat
28561 gggccctcag cttgtggctt gaatatcttt ttttgttttg ctttttttt ttgggggggg
28621 ggtgaggtgg gtgggcagca gtatattatg aatctagcta gtaagcaggt gtttaaaaaa
28681 acgaataata aattaattct agaacgctcg taataggtga cttagctggg caggggtggc
```

FIGURE 6L

28741 acatgccttt aatgacaaag ctccgtagga aggcaggtgg ctctctaagc tctaggacag
28801 cctggtctac agagcaagtt ccaggtcagc cagggctaca cagagaaacg atatttcaga
28861 aagattaaaa aaaaaaagtg tctcagactc caaggagagc acctaactta aaaaaaaaaa
28921 gacttaattt tatgtgtatt agtgtaaagg tatctcaccc ttagatctgg atcccttgga
28981 actggagtta caattgtaag ctgccatgta ggtgctggga attgaaccct ggtcttttgg
29041 gagagcacac gtgctcttaa cctctgagca atctctcgat tcctaatagt cttttaaagg
29101 tctagtacct ggctggagag atggctcagt gatttaagag tgccgactgc tcttccgaag
29161 atcccgagtt caccgagttc aaatcccagc agccacatgg tggctcacaa ccatccgtaa
29221 gaaatctgat gccctcttct ggggtgtcct aagacagcta cagtgtactt acatataata
29281 aataaatctt aaaaaaaaaa aaaaaaaaaa agtctagtac cttcatcctt aaaagcagct
29341 ggctccggcc aggcaggttt ttggtaaact ggaggcatag taccaatcca ggatagcaca
29401 gaaataagac cttcagcgtc atctagtgaa gctccctggg catctggtaa acaaaacccc
29461 cggggcagga cgagattgga aggtgtgctc ttccaacgac cttttgacta taaatccaaa
29521 tacccattgg gttaggctac tgggaggctc actgggtctt gagttgcctc tgatttgctt
29581 ctgccaccta tgtctcatcg atcagttctt cacccggtgt cctgattttg tcactgagtt
29641 cccccattct cagtgttcag tgaggcggct acctactctc ccaggagtct agaatgtatg
29701 gcttggttga ttttccaacc caaaccattc atcaccttcc catggcaaag atggagagcc
29761 agcatctcag agttacctgt gggcaaccta acgactcagc accttgcagc caggaacagc
29821 ccgattttcc ttggttctct ctccagcacc ctcaggcacc ccaactgtga agcactacca
29881 aggacaggaa aatgcacgca gcacgcaagt ttctggcaac cccgccccac ccccagactc
29941 acacatacca aagccaccct ggccttttgt caacccaagg tccaggggcc aagcctgtga
30001 agcagccctg agacttgtgc ttcatgcctc ctgatttcc tctagctgag taagtgaggg
30061 gaaagtagct tcttcaaact caacagcaat ttgcatttgg agaaacccgg ctgtcagttc
30121 tcgtgctgag cattcccgag tgacacacac acacacacac acacacacac acacacacac
30181 acacacacac acacgaggct cagcttcccg gctgtcagtt ctcgtgctga gcattcctga
30241 gtgacacaca cacacacaca cacacacaca cacgaggctt agcttcccga ggaagtgggg
30301 gatggttcca gagtgaagag gaaaccaact gggagacaaa ggtgcataca gaattctttt
30361 atttaactta atccatgtgg tactttaact actagaaaaa agcagagtaa tagactcaag
30421 tggccttagc tttagccatt caaaatagac aaagtttctt ttttcataat gtaaagaatc
30481 ccgagtatgt cgcagtaaca ggaataaatt cttacaacag aatatacaaa aacattgaat
30541 ttttttttcat ctactgattt tcttttatat ataaacagag ggtttttttt tttaggaata
30601 atttatacac agaaagttat tttatgtaac aaattggcca tattattatc ttttttagac
30661 tttttttttc tttttttaag aaaaaattta acaagaaaac tcagaaatgc attattggcg
30721 atgtgtccgc tccatcgagc cttttgactt ttgttttgtt tttttaaatc ccagaggtag
30781 atgaactctg gcaaaactct tacttcaacc tcactggcat aggaagcaga caggggttgt
30841 caccaggcag gcacctactc cacctgtaca tgtgtctgca cactgcccaa cacccacaag
30901 aaactgaaag accaaaccaa acccacaaat ggttcccaga ccttttttcct gcagtgttag
30961 aaagttccat gtgttttcaa caacggtatc ttgtggaacc agagagacat ggccaataat
31021 gcacggggag ccaaaggaca tggatcttaa tttgaaaaaa gggggcgagg ggacacacat

FIGURE 6M

```
31081 tgtggttttt gttaccagtt tgttctgtat tagaaaacaa tggaccttcg gcgttcgcca
31141 ttagatacag gtaggcacag cattcgttag gatctgaggc acatgtgccc acgggctgca
31201 catcagagtc atgtgatcac tgtgaagcca ttccagtgtc ctgaaaccct cccatctcca
31261 tagtgttgca gagctaggac cagccatacc agccagatgt caccatggag tgccatctct
31321 ttgctgggtg gccacacact gctatttcca tggccagcag ttctttccat ctgtttgggc
31381 tgctacactc cacagggaac agtgagtccc agataattcc tttccccagc aaagggttcc
31441 aagatcaaga tactgaagaa tacagaagta ctttttaaac cactggcatt ccttttgttt
31501 tgtttttatt tttatctgtt ttattttttt ttgttttatt tatttattat ttatttttt
31561 acaaactaga gcagaaagca tgtgggaaag agggtgaacc acaattggtc ctggggagaa
31621 tttcttttta attaattttt ttaagttttt attttttatt tttggcatat tgtaaagcta
31681 gctagtaaac aagtgtcaaa aaagaaaaag gaaacaaaga gggggaaaaa agaccacaaa
31741 cacatatttt tgcacacaca gagagaaaaa aaaagtgttt ttaaattatt ttcggcaatt
31801 ataaactaca aacattttat aaaattattc tatgttctta caaaaatgca atgaaacatt
31861 gaattagttc ttgtaaacca gagcttcgtc aacgactacc cgtaatctac tggacttaga
31921 agccctattg aaaggataat gagtaattta aagaatggtt tactggaaag atgcagacac
31981 aaatgtggac acacaaatca gtgattatga agttctcaca gaaaccaaaa tcaaatcaat
32041 ccctaacgtc atgccccaga ccgacaactc atctgatgag tgtgatggag tctgagtcct
32101 tccgcacgtg acttagctct aaggagaagt ttccagagca ggatgccaag tgtcttatct
32161 gaaaccaaat gcccacagtt gactccccag cctccacatg ctctgacacc ttcagacacc
32221 atcaagtcca aatatggtcc atgcttcttc caggcccttt aaccctctgt cagcaattcc
32281 cgtcatgtca cgatgccggt taccaagggt gcctactgca ccgtcactct gtcatcccat
32341 caaggaatgt tcgtttctct aaatcgccaa ctggtcatcc aagctggaag cccaaagcaa
32401 agacccctgg cctgtccaag gtctgtatct tcagcatctc tggcaagaga ggttcaattt
32461 tacacagaca tcctgtcttg aagttctcat ttgtaccacc acctagttca aagtggactg
32521 ttaaaagttt gaccatcatc actggttctt aaggggtgga tctctctggt ccaggtctcc
32581 caatgcagct gcttagccca ggaaatgaaa agacatcaga caaacataaa agtaacatta
32641 aaaacaaaaa ccaaagggaa aaaaaaaatc ccaaaccgta aattcattac tgctaaaatg
32701 ggccaaagca ttttgatgga gtggtcctgt ctcctcctgg atgccagtgt ttaggaaagg
32761 agatgctttc agcactctgt ggccactctc agaggaccca acgatgacaa cagagggcct
32821 tgggtaagca tcctagactc ctcacccaca tgagctcagt gtgaccttgc caccactgct
32881 tgcttacctc aggcacaggc actgccaaaa gaggtgggct gctaaggccg aggctccggg
32941 agctcaggct ggcttaggac ttggcatcat acagagctca tccatctgtc agcccaccct
33001 aaaaactcct gtataccact ccgccatctg ctcgtctcac cgtgatcgct tttctagttt
33061 atgaagctgc ttttcctacc gttgaacagt cccgagtcat aagaaacagg caggtaggaa
33121 aaagagcaac cttgaacagt cttttatatc tcaaggaggg agcctcatcc catctctgaa
33181 tccaatgtta ggacattcct gaaaggagat ggcgaagcgt gggccccacc cagctcaggt
33241 tcagctctat ctccacgcct caggaagggc tgtgtggggg cacacctgga tgttcacgtc
33301 acctgcatgc tgtgcctcag tggttcatgt gacttcaagc agtgtgagct cctatcagaa
33361 ggggggggttg ggtgggggtg ggctcgagtg aaaaaggcca cgactcagct tggtaggagt
```

FIGURE 6N

```
33421 acttgaagct tgtaaagaga aaaatcagga agaggcgggg aacatcagca tgagatcagg
33481 ctagaactgt ggatatgatg ccttgcaata gtcggggcgc gtcagtccag cagaacgact
33541 gcaccctcgt acaagccaac cttttctttt tattgaagtg tttctggagc attagtttat
33601 gacggccact acgctgttgg tgccgtctct ctacttaaag gaaaaaaaaa aataacaccc
33661 acgcaaaaac aaaacaccaa caactcggac agtttcaaaa ataataataa taaggaaaaa
33721 aaaaaaccct taaaatcaat tgaatgaact gtagaaatcc agttgtggaa aaccggcagg
33781 tatgtgcgag aggataggcc actatcccag agtgtcacct acagtgtaga agaaaaccct
33841 gatcaaacag tatctcccag tgaccctgtg agcatctagg aacccagaga agggcagcat
33901 tccagcagga ggcgaagggc tcctgagctt aaccgaactg ttaggcagtt tctccatact
33961 gggggaaaag attagccacc gcggtcccca gctgaagtcc ccagggcctg taagagcagc
34021 tgctggagtt gaggattgca ctgtccacct gtgagcagca gacggatggg tggacagagg
34081 cagagcacgg ggaaggctag gcgccaacca ctggccttcc agcctcaaga tttggtcagt
34141 ccttgtttag ccctgggggt tgcgggggggg ggggggggaag ggagggaaga agagggaagg
34201 acagcagcct gcaggggggca caggcttcgt cttgcccccc ttttttatact ggccttctgt
34261 cagaagcaga agggggagct ccctgaccgc tgtacctcca agaggaacca atgccaggag
34321 agcaatggtg gcatgccccc gcctcggtgc aggtctcaga ggagcagctg agggggctga
34381 cagggcaccc tgacatgtgc acacattggg actctcaaga caacctacgt gtgggtgcct
34441 cctgccctca aaacctggga gtacctgctc tcttagggat agaatttgtc agtcattcaa
34501 tctgtagaga aagttctgtt ccaaagtcag ccagctgagg atgggccggg gagccccccc
34561 ccactggcgt gctgtgctca tggtgactgc tgggttgaaa agtaggggac caggtgagga
34621 gaaagaccag agttgcccta ggaaaagtgg gcttttggag acagagcagg aagaggctgc
34681 tcatttgagt tagcgttgct ttaaccccag aatccagcct ggcccctctc tgcttcacct
34741 gggtatgtgg cctgcggagt ggctgaggtt accaggatca ttggcctact gtcaggtact
34801 gagaagtgtg agatgtatta tatatatata tatatatgtg atatatatat atgcacacac
34861 acacatgaaa aacaagagtg aggtagataa atgtttgaaa aacaagcccc cccaaaaaaa
34921 ccccccaaaa ctgtcccatc taatacacac atacacagag atacatgtac cctttcctca
34981 gcatttaaat ccataacagg ggcttttcta cagtgattaa aacaggtatc acaaaataaa
35041 ttaaaactcc tacatgaaat accttcttaa taagcttccc ccctcctttt ccctttaagg
35101 gcagaggcta ggaagagcca caagcctgaa cctacagaca agccagacaa ctccagcttt
35161 ccttcctgca tctaatctcc agtcacaact gcaaccatca tcatccaaca gttttcctac
35221 tcctaattta aatatttcca cccagaagca tctctcgcgc tgtcactgct ctggtaagaa
35281 gtgctaaatc gaaacaagac aggacccctc ccccaacccc actccagggg gaggggcctc
35341 caagcccaga gctccgggat tctggttaag gaggaacagc aaggggctct agggccactg
35401 tagggtcagc tctactccac tttgggattt ccggcccggg agtgggcttt atagcacacc
35461 cactaaagtt gctgctcctg gccatgggga gttggtgtct tacatcttgc tcccagggag
35521 gccacccctt cagacaagct ggttctaaag acaggtgggc ctgcttgtga aggaggtggc
35581 agatgggcca ctggaccagc tctgctgcat cctggggact cagcagctat tgtgtgtgtg
35641 tgtgtgtgtg tgaaagatca aatattcatt taaataataa tccaatgact attgtctgca
35701 gttaaaactg ctattgtatt cccaaattgg ggtgtgtgtg tgtgtgtgtg tgtgtgtgtg
```

FIGURE 60

35761 tgtgtgtgtg tgtgaaccaa agcaaggaga gaaagcaaag tgtgactttc aacaacaggg
35821 actagaaaca ctaaaccagg atgtgtggga tttttaacct ttttgtttct gacctgagtt
35881 tgtggcatgc cttgccctgg agcagatgct gtgtgcgggg aagcaaggaa aggagagagt
35941 agggcccagg agtctgtggg ctctggactc ccaccctccc cactccctca cctgtgactg
36001 tgctcacaga gcctatgggt tagagggtaa tgaatggggc tgcagggagc aggggaaggg
36061 agatgtattt ataaaaaagg catcaaacag ttcacggcaa gttatgtcct agaagcatca
36121 gttgccggag aagaggaaga aaaaccacac tctagtgata agcagaggaa gtttcttgga
36181 gtgagcagaa aggaagaagg ggtagacctg aaagtttcat agattaaatc cacaaagata
36241 aagaacaaaa aaaaaatagc agcttttctt ttcctgtaca gatgtataga tgaatatctg
36301 aactgtaaaa aagttataaa actgacatta aagacgatgt gtatgcaaat gtttcacggt
36361 ctaacataga actgagagac ccatgaagaa gtcctagtaa cagaccatgt gaaagctcac
36421 actgcttgga tccactgcct gggcgggcgg ctccaggctg ctgtggctct gaatcccttc
36481 ctcgaacatc cataaccaac agccaggccg agtccccgga acccttтcga gtgtgtggcc
36541 ctcaggggag gggcaggagg gaggtcgggg aggggggacga ggctggtgtg aggaccacct
36601 tgacccacaa cctgaccttc aagcttgccc atggccactt cctccagaat tcttggggtg
36661 ctgtgggtgg gggaggggtg gagaaccagt tctgctttcc cctttcttcaa ggagggcgag
36721 ttccatcttg tccagttctc ccaaacggta accatgcaac gagacccagg agatgtgggc
36781 tgggagagcc gggcacagtg gggggcctca gcacgtgtct ctcaaatgtt atcatcaacc
36841 agacaccatg gttcatccca cgcctctgga caaagggaaa tcagcgcagg gagtatatgc
36901 gtgtgagaaa aaccaaaccg aaaacaggat tttggcaaaa atggcagcgt gaaaaatgat
36961 agccacggat gaacaatggc ccttttaaat tttggggtga ccctaaaaaa ggttaaaaaa
37021 aattccatct cagtgtgtga attttttttc tttttctttc cttttctttt ttttaaaaga
37081 cctacggtgt caggcaggtg tatgcggggt gatgaggagc cccaggggca gccattaagt
37141 caatctgatt ttttttttt ttttaaaaaa gaaggcttcc cagatgggcg ttcacaaaca
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37261 cagagaggga aggcagagga gagaaaaagg cagagaacga agagactcaa ttctcgagtg
37321 tcctgttgct attaagtgtt gtcattaagg tttgcagagg cccatgtcag ttaagggttc
37381 gggtaaagga aataaaaagc tgcttgcata ttgaaaaaag gaaggtccca aatgtgttta
37441 ctgcagagaa gccgtctccc gtgggcagca atggcaggtc tgaagatcca ctgaggtaca
37501 ggaggcttgt gaatagattg ttacaacctg ctctcccctc cccgcccccc cgcccaccga
37561 gtgggcgcac acacgttact gttggcgcgt gcttcggtgt gtccgaggat cagcaggtcg
37621 aggactgggg cagaggcaag gccctctcgt tggcgcgtcc cccgttcatg tgagcgtaag
37681 gctgtctctc atcaaaactg gcgcggagaa cgagcacgcc agggcccggg ccattctcag
37741 ccttgtgtcc tgagtgtctt tcaggcagag gcagggaggc tgaggaggcc gaagggtcca
37801 gtgggacgct ctccatgttc tcaggctcca tctccagctc ctctggctcg ggaggcttgt
37861 tctcctcgct gtagtagaag gagacctcct ggaagctggg ctccatctca tccttgatgc
37921 tgccgatgat ctccaggaag gagggccgca tcttggggtt atactgccag cacatgcgca
37981 taagttcaaa cctaagggag tgatggggaa gaaaggaatg agctgccaga gagacccaga
38041 agaactgtac cacctctgca ctctctgctt cccatctgga tgcctctggc atcctgccat
38101 gtatcttgcc cagaacccag gcccagccac agtgccaagc ccagactcac ttcaagtctt

FIGURE 6P

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38161 ggttcaccga ttccaccatg gacggttgta ttaatgatag cactgctaag agataaaacc
38221 cacttcctgt ctaagcacct cttctggcca cacattaacc agaagaggaa acctctctct
38281 ctcactaatg agaatcacag ctttcctgac aggcaccatt ctctgtatct cacaccaggg
38341 ctatttctaa gtttcttcct ggcaccaggg cgcccctggc agtgggcctg agggaggagg
38401 cggcaggggt gctagacaga cggagcacat atcccaagct tgctatctca cgccagcacc
38461 tgctcactga ggatgtccca tgaaggaaga tccctgtctt gaagatgtag gatgcccagg
38521 agcagagttc taatagaaac ttcaagtcgg atgccaacga accaagggaa gtcctaagca
38581 tcattttctt ctacaaacaa ggccaaggta aaaacagtat aaagcccatg acgtacctcc
38641 atcactccca caaggtcaca aacctttgca aagcttcctc gtcctcgaga gttacatggg
38701 ccagctggca cacaggacag aagagaaagg ctgctcatgc agccaccgtc ctgaccagca
38761 aaggcctggg agtagacagt ggaggagacc ctaagcaagt gaaggtgtgt attgctgaca
38821 cgtgcaaggc catgtcaagg accccaatgc cccagtccca tgggagtggc aaagtctacc
38881 ccagtgatgc ttgcttagag agatggtaaa gccttccgct gaggtccgag ttgcaagtgc
38941 tgacagtgtg tgcagaatat gtccactgtc acgtccttcc cctggaagtt tacagcctca
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39061 ctgcttcctt gtttatctgc atgcagtaat ctgcctctct gttcaaatat atacgctaaa
39121 catactgagc ttccagagcc cagtccacgc agtccccgtt tctctatacc caagtgcaca
39181 ctctttgttc attcccttga tgccctcgtc aagtcatagt tctgcaaccc aggccatgca
39241 gtgaaccaca cctgggctct gacggatgga cagacacaca ggcccgacag aaaacaagga
39301 cagggtggtc atgattctga gggaaagggg tacctagcag ctctcaatca caggcgtgtg
39361 agaccaaagc actctccacc tatgctcctc caggaaactg tgttttataa aaactcctgg
39421 ctcaacagac gctttacact aaaacccaca aatggaagtt cgaacatata ggaatctcaa
39481 agcaccctga acaggcttct aacattctac caggctgatc actgggccac caggacactt
39541 ctttacaaag caaataatcc cacaggggta aaggcgtgtg aaagcaacct attggtaggc
39601 atgaagttgc ctgtgcagag aaagccactc ttgcccatct ggccagcttc cttggactct
39661 gtaggatcaa gtcaggccag gtggaaggta gttatcttaa aactgaaaaa aggtgcattg
39721 gagatccacc tccaagaatt aagcactctg gaggcccagg gtgaagccaa ccaattacag
39781 cggagccagg tgcagcttgg agcctgttgt tagcggaatt gtaccagagc agagctggtt
39841 acacagcacc tgtggctgtt tctaagctcc tttgtaggct gagtagttga gacagcggct
39901 gtttagctag gaaccttaca atatttactg cctactcctc tggaggtaaa gaaaaatccc
39961 aattaagtgg ccaatgtctc gacggaggaa aacaaactgg accaaagacc aggctaacta
40021 ggtattctca ctggctctaa gtgactggtc ctagtggcac atgacaggtt gcaggtaggt
40081 actaaaagct ctaggcccgg gagtcacgtc agtccccgag agccagagat gtctctttac
40141 tccaatgatt acaacacatc ctcattgtat gcataaggga aaagcaccaa ccacagcatt
40201 tgatcatttg tctgaagtca cacagggagt gagctggaac ggcgtgaggc tgtcagacaa
40261 tgcagcttta ctgtaagtaa ccatggtctt gctagcagac ggcgctctcc cgactgtcta
40321 cagacagtca gatctcctga gccggcttgc tctggttagc tgctgcagaa gcttgttctc
40381 cccggtcccc atcatttccc gaaggattaa tcggaatggg aagcagacac aaggagctta
40441 gctccgtggc caggctgcaa tttcctctct ggctgacagg cctagccctg aatagaaaag
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FIGURE 6Q

```
40501 tgcaaccggg ggcaagaaca tgagatgtgt ctggccccaa gccccgtggc caggggtggg
40561 gggtggggct gaggaggtgc cacgggcagg gtagggatga ggtgacatca gtaaaaacaa
40621 gccatgtgat gcctctttta aatcatccca gagtcagccc ttccagggct gcccataaaa
40681 ggaagtcttt tttgctctgt gcgatttaag accttgtttt ttttttgttt tgttttttt
40741 aaatactctt tccacaagaa aactctccag tagactctgg gattaataag ctgataaaat
40801 gctccctcta aaaagcacac tttaaaacca ctggacagct ctgatgagct ggagccgcga
40861 tttacagaat atgtccctct gtgaaggtgc acacctatcc ctctagaagt gagtgctatc
40921 ctggggtgta cgcccaccgc tatgcccatt cctcacttgg cttctgagcc cccaagcaca
40981 ccccgtgtct tcagctggac aggctgccat ctatgtgagg cactggcaaa ctgaaatatg
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41101 gtgactctta gcagggatca gactttcaga agggcctacg ggactgagtg ggtcctcctc
41161 tagcatctca agcaactaag gttgttttag ggccaggacc tagacgggga tgctatatag
41221 cccagttgct ggcacacagt cgatgccagg gaccgtccag cagacactgt cacctgcctg
41281 tgatgactct attcaatttа tctcgacaaa accagactgg gattcccagc ctcctggggg
41341 tggagaggaa aagtacagaa gtagtcagat tggactgagt atgtctcagc tgcatctgag
41401 ctggtgacgc tcggctagta aaacgttcaa gttccttcct gaatcccgca tcccgaagac
41461 ttggcatgtg agctctggag atgttaatgg atcaaatgga tcaattctgt ggctgagctt
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41581 gtgaactctg ggactggccc ctgacctcag cagggttcac tgacaaatct gtgtccaaag
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42001 atcctttcac agaacacatc ttcctctcat cagcgtctca gccaaatcag ggcaccacac
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42361 caaatgtttg ctccagcata aaagaaaaga aaaaaaccaa caatacctct cctgtgacca
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42541 gaggcagcca tgctcctact ccatcctttc acctttgccc acatactgac tattctcgca
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42661 aacccagagc ttctctaggc aggccccctg catcctgtac gccttcggag gtcagtttag
42721 aaaggccaca gtggcagtgt tctccgtgaa gatgctgcag ggcacagcag gccacggacc
42781 agtcagtggc tcaatatggc ctgctgtcta ttcagttttg taaggccctc ccaagcaaga
```

FIGURE 6R

```
42841 gggtttttt ttttacact tgccaacagc tggggcaaaa acaaacaaat taacaagtcc
42901 cccacgcccc acccccaaat aggagtattt tataagaaga aaacgagagg aattcaaatt
42961 ccaatataaa gttttagttg ggcaccagca gtaacactgg ctgcaatcca agcactaggg
43021 gagtttgagg caggaagatt atcctaaata cctgggctac actgactcca tccttgttga
43081 ttcctgaatc atagtggcag agcagagggg ctggaaggaa gagtgagcgt gcggtcccca
43141 gcaccaccaa tcctctccag tgtattagag aaatcctctc agtctatgga gtggtccaca
43201 gagaagccac ggcctctccc actacacaga accatcactg ttcctaccgc cctgtagtaa
43261 atccgatctc cttacaatca ccccacgtac cggagtatct tcatctgcgg gaagccctgc
43321 ctctgaccag cagctatctt ctggagaccc tgagctagct agtgtcacct catcgagctc
43381 ctcctaggtt tcattagaaa gcctgtgaga tgacattttc aactgttgga gcctcacggg
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43501 ctgtgctctg cccaccacct gcactgcacg cccaacctct ccatctgtac attgcctcac
43561 catccaaggc gccacgagag tgagcgctgc gctggggaag agaaggccag gggtaggcag
43621 agtcttttgt gtagaagtga agaaatcttg acaaccccc tgggattctt tcactagtgg
43681 agctgaacct gttttgaagt gtttctggga aactgtatgg gtcctgacat atcagtggga
43741 acctgctttg atgcttaacc ccgagatgca gagcaacagc cgagccccac cttaacgtgt
43801 gcacatcaaa tgcaagtcca ctgctctcaa cctgtactcg atgagccaat cggaatacct
43861 tcatgtcttc cttgaaacct cactccaaga agtgccattc tcggggctgg agagatggct
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44221 tcattctcca gacccactga gccaccaaca tcagatgaca aagaaagacc tctactcaag
44281 agagtacaaa taaaaggccc acatgtggaa agattcttcc ccaattttgg caacaccagg
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44461 tgctgtgtcc ccttgacaca gttcctcatg tcgttgtgac ccccaactat aacactactt
44521 tataattgta atctgctact gttatgaggc aaaatggaaa catctgtgct ttctaacggt
44581 ctcaggtaac tcctgtgaag gggcaagggg tcacgactca caggtagaga acggcttctc
44641 taatggctcc ctttcacttt caagccacaa agtgagactg tgcgctctga cacacctttt
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44761 agccaatgtg aaatgcttct ccttgtaagc tgtttatctc agggagtttc tcgagtcaca
44821 ctggctgagc acggaggtgg acgtgacacc acgtgtgtac tgccatcgag tgacaattct
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45001 taggtccatg cagctcgaag ggattaagaa gacagcagat ggtctgtgac cttgtgctgg
45061 ggctctctga gctttagtct acccgtgcaa gagagtgact cctgaccaca gagctctgtg
45121 tgagcatgct gtatagacct tccaggggct tggggagagc tttcaaatct ggctcagcag
45181 tagtaactaa cttgcatttt tgtcttaaaa attaaatttt gcatgaaaaa gatgagccag
```

FIGURE 6S

45241 gattgctcat gtatttcaga gatgggagat gggggggggg gggtagtggt ggctgagacg
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45361 taaggagcag cacaaagtca cagatccaac aagctcagca gcagcaggat agagcctttc
45421 taatcctctc ctgtacccac acacaacgga gtgggtggct ctggaaatac atacagcata
45481 tcagggcagt tgtccggctt gtccagaagg ccaccctcca tgacgaaacg aagaacttgc
45541 tcgttggaca agccctggta gggctgctca gccagcgtgg cgatctccca gaggacgacc
45601 ccgaaggacc tacaggtgga acagaacagg aacagctcag aaagggatgg gaagggccat
45661 gtcccctcct tgccagcatt tcttagactc tgggtcctga aaaaaagtgt cctcaatgtg
45721 acgactgcac tttgtggaca tcaaaccagc cagcttgcta cgtgtgggac atctgttccc
45781 ctttgtcact gctaaggctt cctatagggc tactgcaacc cagggctgag gtaattaatg
45841 ttaggggctt ctaacatctc tcacagtttt aagagcccga tctacagcgg acacattcag
45901 tgtctggtcc cagccattac ttggacataa gccaaattag ctctagttca gcaaggaatg
45961 cagaggacca ggtcccagcc tggccactga cctgagacag ctaagcatct caactatctc
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46081 cgcaagaaga atctgatcag ggttcttaaa acaatgggta tcttgggctc tccaaagcaa
46141 ttctgacctg ctggttgtag ggtagggagc tgggcctgga atgtctcaaa gttctgtagg
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47521 caagtcaaac aaaatccttc caacttttct ttggattttt acctacttct gactgtgaat
47581 tcattctaaa atgactgcaa ttcctctagc aagcagaggt tcaggcagag ctgagcatcc

FIGURE 6T

```
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47701 gccttttctc ttcacgcatt ttcttattgg tttgtaatgg ctacgtaatc caagtggagg
47761 aaacctgcag gaagcaccct gtgcgcctct ggctgtggca tgcagttgtt acccagagtc
47821 gggggagaat gagtctgtgc tcactctttc cctatcctgt aaggtgatct ccaagcttcc
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48061 atattcaaag gctatttcca atttgcacct gtcttccaaa caagatccaa ggctcttgac
48121 cgggaaaggt tcacgaggct aaagaactga tgtcagtcac tactgagata gtttctctgt
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48361 tttccaagga actgcagtaa acattactac agagaagtct ttgcaccctc tggtcagtgt
48421 gctactaccg caagacactt attattaagg aagatgcttt gggtcaggaa taatggacat
48481 cgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgaacaga
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49621 tggtgaatgg caggcttgct tttttataat ctcacattac tgtgtcttta tccatttttg
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49801 ggtgaggtac aaaaaaggca gagcaaaccc atgtagggtt tgctctgcat ggatgttaac
49861 ccaacacaat tgacttgcac cgctgtctga gctactggct gcctctcttg aactgattta
49921 gggtgtgtaa tccctgagat gggggcactg ggggacactg aggaatgcag aactcgcccg
49981 aggaggaaaa aggaagtgct taaatctcat ctctgaatta atccagagac atgcaaatga
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FIGURE 6U

```
50041 gaggatctgc tttgacttgc ataaaagggg aattctagaa aacaatctct ctccctaaat
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50161 aagaaaaatc ataattataa tagaaaatat cctcataaat gcgccacatg gttaagcaga
50221 aaatataatc cttactgatt tggatttaaa atggcaaaaa gcacacgcac acacaaaagc
50281 atttttccaa ctgtaatgca aaatgggacc aaagcagcct ctcggagttc ctggctgtgc
50341 tgagaagggt gcacagcagg gtaagatgag gacaggggca caggcttgct gtcccagccc
50401 gcctcctcct ccagctctgt cccaatccac tctcactcca caggtgggga aagatggcac
50461 agggagggaa ggcacctgcc tcaggccact caggagcaca gtttcctctg aggactaaaa
50521 tctagatccc cacacataag ggagggatgg gaggcaggaa ggaccacaaa ggctggttaa
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50701 cttcagtaac tccaatgact gacatctgtt ctgtaacaca gctgcatgcc aacaccccta
50761 actcctgcaa tcagcaaaga agagagcccg actttggata cctctctaga gatgacaccc
50821 atcgcttact aagaggccgg aatggctcat gcaaaaacca cttctagggt tgaggcaagc
50881 agaacatctc caggacacaa gctcaagagg cggccaaagg ttagtggctg atcgcttctg
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51061 ctacttttt ttttttttt ttttgaagta aaagacaaaa aaacaaagcc aatatacaag
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51661 aaggtgctct ccgggttaca gccaggaata gacagtcaca ccgactacat acatctttgc
51721 actcaagggc gaggcactgc tcctctcgga cataatgaaa atctctccag tggcagacta
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52261 ccttctaccc actggttgag gcagggtgtc cctatcaaac ccaacctggt caacatagat
52321 tgctctgggg atcccaactc atccttccaa ggctggaatc acaggtgtgc tgccacacca
52381 gcccagcctt tacctggctt ctgacgacct gaactctggt ccttatgcct gtgaccaccc
```

FIGURE 6V

52441 cctccccccct agtcttttct atttggagca ggacaaaaat gatttgaagt gaatcagcaa
52501 gtttaggcat taagcattct cagctccagc tagtttccat gttcctttgg cttccgccat
52561 caccaagtgt gagtaagagg aaggacagag aacccgtaca aaggccacgt gaaacagaca
52621 cacttcctaa gtggattacc acgagctttg cttcccgtgc aagctgccag gacttattcg
52681 tcttcattcc cttcttctaa ggtacaaaga taggaagact aatgctttcc tcttggatta
52741 ctgttttcta cgggcactga ggataaccac agttcaggtg gagttcacct tggaggggac
52801 caaggacact gagcagcaat gaggaccaat atcatgtctg aagaggaggg caagatgctg
52861 ccttaggaac tgaaaagaat taacctaaga agtggtaaaa tcataaacaa acaaacaaac
52921 aaacaaaata agataagatt tatgtctaag aggctgatga gaatggctta gtgggaaagg
52981 tacctgctgt caagacaggg ggcctatgtt catgtcccaa gacaggtatg gtaaaagatg
53041 aaaaccaact ccctcaaggt ctaagtaggt atgcacatgc atatgcatga acacacacac
53101 acacacacac acacacacac actacacaca tacaaacata aaaaattccc aaagctccgt
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53281 gagcatgacc aggcttggag atcacactat ttgggctagt atataggccc tttgtgctct
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54001 tatatacact gaactgtgga gtatacattg atgctaagat atatgtaagt tatttttaa
54061 aaaattctga catgagttag acaaaattta gatctgatga atttaaagat taagttttac
54121 ttccgaaaga gactttcgta atccaacctg tctctttaca ttgaattaaa attttgtttt
54181 atgtttgtgg gtgttttgcc tgcatgtgtg tttgtgcact acctgcccac ggaggcccat
54241 ggaggccagc agaacagtga ataccgacag ttatgagccg ccacgtgggt gctgggaatc
54301 cacccagggt tctttggaag agcagccagt gctcttaact gctgagccat ctctatagcc
54361 ctttctctct ctacatgagg aagcggaggc ccagaggcat ctgttaactg aggactggag
54421 gtaaccaatg gcaaaaacag ccccgagagc acaagttacg ggtttactct gggcatgtgt
54481 caaaggcatt aagcacattc tgatgttagg aggtgcctta aaggaccact ctccagtctc
54541 cttctgtaga ctgggtatta ctggggtagg atgctgctgc tgggagaaac aggcatagct
54601 ttgtggctct gctatcaatg catacaccgc cttgtggctc tctcctgaaa cttcagaaac
54661 acacatgagg acatttgtga acaggtactc agaactaaaa tgaaggaacc atccatcact
54721 tggtagatga ttacgttgtg gaggaaaaga aaacgaaagc ttctacagag aaggggagca
54781 aacccagaaa gggcccgaga agaggaagtt ccccttacag cgaatgcaga gacaagctgc

FIGURE 6W

54841 ttagttagcc acaggtatca aagccagggc cgaagtgaga gcctcagagc ctgaggcagc
54901 cccatgaaag gcatttggtc cagcaatatt tctcaacacc cccatcagtt aactcttagt
54961 gaggacttag aagccaaact taagccaggt gcttgtggtg catacctta atgccagcac
55021 ttgggagaca gaggcaagcg aatctctgag agttcgaggc cagcctggtc tacgaagcga
55081 gttccaggac agccggggct gcacagaaaa aaaaacaaaa caaaatgctg tctcaaaaaa
55141 caacaaacaa acaaacacaa aaataacaac aacaaaaaag aagtcagact cacatatgct
55201 aaaaagctgg ctgtgggcta acacaacaga aggggacact ccacagtgac taatcaaaaa
55261 attacacagg acctactcag gttcacagtt tgaaaatctc actagcctta agcagaatca
55321 tgcagctgga atggttatca tttaaaagcg caggcacaat actggcttat tgcctagcct
55381 ggggagtagg ttcagggttt gagaagtgtc tgaagcagtg tcggggcaag gggagagcag
55441 tgtgtgccat caaggtaagg atagcatgct cacatgtaca cgtgtgtgtg tgtgtgtgtg
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55561 tgtgtgtgtg tgtgtgtgtg tgtaatgggc tcctgaggaa acagtggtct cgtgcacaga
55621 ccgggctgcg agtcactctg gccaaaacct ctgacaacct gaagagtgac ctttattgag
55681 tacttactga aaaggttacc agccacggtc atgaccctga ggtaaagaag aggctcaccc
55741 cgaggacctc gagagtaaac gtatgctagg cagtcaagtg tactggaaag tcagtggggg
55801 aggccagccc ggcctgagtg ggaagctgtg ggaagggttg gccatgacac gtggtagagc
55861 agctggggtt ggtgtaagat gtaggcaggg gtagcgggga tgcagaaaca agagcacaga
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55981 tacacttgga caatcctata tagagggaac tgacaagaaa gcatatctca aggcactcaa
56041 ggctgagaag caaatggact taaagacacg tttcctacaa gccagctcct gaaaaaagtg
56101 gaccaagcaa gataacacag cgaggaacaa aactgacctc cacttctggc ctcagagacc
56161 ggagataact tttgagatca ccgcgtgtca ttagttccat gatgaccagg gtgggctggc
56221 cttgggatac cacacccagc aaccggacct ggaggaatca agaaaaggac tcagaggggg
56281 agggggggcat cccacatgat gacctacgcc tctcggaact gggtggtgct ggggcctgta
56341 gccaggagca gagttctggt gggagggcga gggcgaggct cccacctcaa gggtctgtgg
56401 gtggcaagaa tgcaacgggg aaactaccca ctgggaagag ggcaaggcaa caattcgtag
56461 ctggccaagg acatacaggg tggtcctttc tgtccatact ttctgtccat gtctcatctt
56521 ggcttcttac cacatggtga caattgaact ccttcatcac cgaggcctcg ttgagaaact
56581 cgattctttc acgcatactt gcagcctcgt ttaccgtctt gatggccact ctggtttcgg
56641 gttcatcctt gaccacaccc ttggccactc cttcatagac catcccaaag gacccttgtc
56701 cgagctcccg gttcatggtg atcttctctc gagctacctc ccattcatca ggcacgtaca
56761 ctagtaacag acaggatgga aacggccctt agacagagat tacaagatgc tgttccctaa
56821 gacccaccaa ggagaacatc aaggtacaaa cagtccagca cgggtactca atctctgagg
56881 actccatgac actttgaggg tggtactcgt agctaagaac cagaaggaaa ccaagaaacc
56941 taagatagga aaaccaaatc aaaccaaaca acagtggttc ctttttcata tccttggcaa
57001 aaccccaacc caacaaaata aaaaaagcaa attagcccta agagacaaag aaagtgggac
57061 ttctgttttg cctgtcttca tcaagggatg gaaatgtagg tcagaagggg agaacagtgg
57121 gaggggaaag gaccaaaggg ggtcaaatct cctcctccct ggatgaagcc agaggtgaga
57181 aacatcctct gcatggcctg ggtgccagtt tacaggccac ccagccccac tgtaggcctt

FIGURE 6X

57241 cagcgcttga agtcgtgctg gaagtaagac atatactgca ttttaaagac ttgcttaaaa
57301 caagtaaaaa aagataactt ttaaaagatt ttaaaattta cgtatacatg tgaaaatctc
57361 tctctctctc tctctctctc tctctctctc tctctctgtg tgtgtgtgtg tgtgtgtgta
57421 tgagcacaca cacatgcaca gatgtgaggc accacccgtg tttgggtgcc tgggaaaccc
57481 agaagacagt gttggcttct cggacctata gttacagatg gcgggaggtc tcttcacaga
57541 ggtgctggga actgaattag agttctccag aaggtcagca aggctctcaa ctgctgggcc
57601 catttttttt tccagctttg tattccaaag acttggttaa agcaagttta aaaagatagc
57661 ttttatatta actgttggat gttgtgggct aaatgaaaat tctaacagat ttatctcatc
57721 agcttttaca cttaaaaaaa catggctact agctgggtgt ggcaacagga aactgcagtc
57781 ccaccccagc ccactgggca tggaggttgg agatggggtc tgctgaacta aaggcatctt
57841 cagattgtgt ttcaaaacac caagacaatg tgtcagccgc ctgggatgtc tatcagttca
57901 cgcacttcat tccacttctt ccatagccat gtccgacaac aagctcaagg tggctgagag
57961 ggagaaactc agtcaacact aaaggcagag actcaagaga agagtcctca gccatcaaaa
58021 gaaaccgcag aaaaggagat gagaggccag cccccacccc cacccccgca gagcgctgag
58081 gtaggtcttg tgcactacaa gcactgtctc cctatattcc tccatacagc tgtttaactc
58141 tggaagctgc agaggttgga tccagtttaa cacaccctgc tgccccttcc accgagatct
58201 agtgacgata cagactgcct gccttttcca cctgagagga aggagaactc acacgttgat
58261 gaagaaaaaa gcagggttgg gagatgaaac ccagggttca aatcccagat gattcaaggt
58321 gctctacagg ctgtaaaatg cagtttaatc ccagggctgt gctgtgttgt ttttcaagtg
58381 atttgactta gtggaatgca tactgtttta aaaccatcaa ttttgtgaat ggctgttttc
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58501 ggaatcaaat cagggtcctt ctagaaaagc agccagtgtg tttaactgct gagccatctc
58561 tctagccccg gaatgcatga aagtattaaa acttaacaca agaagccaaa ctcttgccta
58621 acacaggtga agcctaggag ccccttccca ggggatctct agtgagggaa gtgagcgctg
58681 ggatggaggg ggactcagta gtgaccccac ggctttggcc tgcactctgc aatgccagga
58741 acctccctga cacggacctg aacagaattc cttctccagc ttccattttt ggttatgctt
58801 gatctggttt gagaaaaata aataaacgaa tagttctcag aaggaagggg gaagagaagg
58861 aaagaaaata agagaggcaa gtaagaaaga ccaaacacag gctccatccc ataacgccag
58921 tgggtacagc gagaactgaa atcatatcaa attaatacgt aagatctgga aagagaatac
58981 ctgctccatg agaaccataa cctaacagag ttactgacag ccctgtctaa cagaggatgg
59041 ccagcaggca tggcaagaag gaagccctag cttagagaca ggcctgggag gggaatcacg
59101 gctgtgtttg tttttatgct tttagatgcc gagctgcagt tggaggtggg agaccccacc
59161 agcaggtcat cacggttatc agtcaccctc agagcacaag cccttacttc taagtgatgt
59221 cttaagggaa gggtgtttat tataaattcg gggctgggga ccccattgac ttgtattttg
59281 aagaatggaa catacatctt gtggtggttt gaataggagt ggcccccaca gactcacaca
59341 tttgaatgct tggtcattag ggagcagtga tacctgacag agattaggag gtgtggcctt
59401 gttggaggaa gtgtggcacc gagggtgggc tttgaggttt caaataccag gcctatgtct
59461 tgctctattt ttgctgcctg atccagatgt agaactctta acccctctcc agcaccatag
59521 caccatgtct gcctacatac catcatgttt gctaccatta caacatgggc ctaaacccct
59581 gaacctgtaa gctcctttaa gccagccact ttccatgaga agagctgctg tggtcaacgg

FIGURE 6Y

```
59641 tgtctcttca cagcagcaga acactaagac acatacttat ctgtctactc acttactctt
59701 acttactggc tgatttgggg acaggactgc tctatcttgt tcatacttgc cttgaacttg
59761 ctatgtaatc caagctagcc ctgaattgac aacttttctg cctcagtgtc cccagtacgt
59821 ggattccagg tttgtgtggc cacatttggc tcctgtgcat gtttttgtat ttcatggaat
59881 atgtatgtct ggtaatttct caactagaat tctgtcttcc atgggcctca gacaacttgt
59941 gaccctgcag aggctgagct tgctgaggag agcagagggg gaaaggtctt tataacacct
60001 ctctgtaagg atggggacca ctgtctccat ttattacctc taaggatcca ggctggcttt
60061 taatgagaat caactacacg gcttgcttgc tgcagagcat ggagttaaaa gcccatcaca
60121 tccattccct gggaggtccc tgaagttagt ggtctcaacc ctttttctaa actcaatcca
60181 gctgccgact ttagccagag tacctcagct ttgccagcca gagctgttca taaacttcgt
60241 acaatgttat cagcactttc ctgtagggca ttctcagtgc actcttgaca acagcaacat
60301 gcagattaac tctgggagaa agacgttttt aaagcacctt tcagatgcaa tgtcactttg
60361 tagctctttg aggcaaaagg cttgtgctgc tgctgtgctt gtcaaaaggc caaacaaacc
60421 aagtgcagat gaggtgacag tgttctcacc tgttgacctg ggtagtgaca agtttgttct
60481 tgctttgttt tgaaggggag agggagacta tttctctggc acctcttttc tcttttataa
60541 ttattgacct agacacaatg gctgcacggt tctggctagt taggggacgg aggcaaggtg
60601 ttcagatcat ctgaggccag gagtttgagg ctggcctgta taaacaatgc atatttagtt
60661 tcttgatttt tgcccgtttg ctttcttgtt tgttttggtg gtgtgaggac agaacccgtt
60721 ctggaacacc gtaggcaaat gctctatcac taaactacat atccaaactc acttcatttg
60781 tttgtttgtt tttaggagaa agatagtctc cgtaagtaac tatgtaacta tgctttcaag
60841 tgtggtgctt acccttctag tgtattttct atgctttata ggcacaaacg tatgcacata
60901 tgcctactta aaaaataact ctgcaagacc ttttgcaaac agaaataaca tcattattct
60961 gcacctgatt caaattcaga agaggctgtt cttgactggc tttactatac acataatcca
61021 gttataaatg attaaagaaa ccatagtaaa accatacgca cttacatggt gcttttaaat
61081 tacaaagggt tttctctttt ttttttttt cccatgtgag caggataatc aatcggactg
61141 tgtcttatct gggccgcatc tacttacact tctggagcaa agaaacattc ctcctgaaca
61201 aactcctgcg ctgcacagac ccccatctaa ccagattccc tacatagccc agcaacctca
61261 cagctagctc ttccatacac cacatcatga ggattcagga ggaaggcttg ggatgtccct
61321 tgtgcagact tcccacggct cagctgtggg agcctgaaca agtccttctc agagattctt
61381 tttttgcctg catctagata gacatgagaa agctccaagg gctaatcgag gagaggaccc
61441 ctccccagct tacttagaag gtctgaagcc aagcataagc gctaggggaa aaaaagagac
61501 cagtagctaa aacacaggtt ccgagtcaga acttctgagc catttaatta aatgactttc
61561 attagttact gccaaaggga atgtaaatgg gtgcataggc tgtatgaccc taatcaggat
61621 agaacagcag agggattcca agatcataca acgctatata gccctcactg gccagggaac
61681 gcctgcagcc ccaccctgag ttgataccca ctcaggatgc ctggctggct acagcagtcc
61741 tctgactaga cggtagtaat tagaatgctc ctttcactct gatgccacac ttcaagcggc
61801 taactgaact gcttagcaga ccggccaccg gcatctccag agcctggttt ctactggggc
61861 atctgagagt cccagaatgt ctgacagtca ctgagtgcta aagatgttat taaaagacaa
61921 gaaggaaatg gtaccaaagg cagatcctgg gacaaaggta tctcaaaatt acgcaacgct
61981 tttctccagt cagcacctga cagctcccat attcccacac cttggccagg acgcttacca
```

FIGURE 6X

```
62041 tcagctgcgc tgaaatactc ggggttcaca gaagcataca gcactccatt gcccaacctg
62101 ctgttatttc tgtcaaaaaa aaaaagatga aaaccaggtc aacaaatccc atctctatac
62161 atttctgtaa atacctttte ttttcctttt tttctttctc acgagttatc ttgagcaagg
62221 gacgcaaacc atgatcactg ctgacgggac ccttgcctgc actcctgatc caggccccgg
62281 tatctgagga caaatctttc cacttttgcc ctggcctcag attagagctt ctaaagaaac
62341 atttgtttct ttgcttcact ggaaataaca aggcccactc catgggaagc taaactggca
62401 tgcttggaga agctcttaca aggcagcaat ctgtgtgcta gaacagccag aaagcagacg
62461 acgggtacag agaaggaagc aacccctctc ctgttgctgt tagtcattag gaaatgtcct
62521 tttttccccc ctgaagaatg tctgactagg aactctggct gtccagtctg catggtattt
62581 tcccccacag acgagctatg ttcaagttca aatcatcaag ccaatgcgcc acaagtactg
62641 tcttccgctg gcccaggcac tcacctcttt ctatggaaga catacagcat gataaccagc
62701 cccccaacga tcagcaggat ggcaaccggc agagcaatga tcagatgcat gaagttctca
62761 tacgtcgctg cagagacaag gaagaaacag gaagacgtca cgcacgaggt gaataactgg
62821 ctcacttcat ttctgtgtat ggttggaagg atgataaaac cgcctctgga atagccttta
62881 ctcccctcatc tcacaagagg agtcttcgag gagtcttcta gtgctgggac aagaccagca
62941 gacaaactga attgtttgga gaaaggtaaa taaatacaga ctgaagcaca cactccttta
63001 aagcactgca tattctgaat acagcaagta attctgaagg caagcccttc ctgtgtgtag
63061 ttttgtggaa gtttagctga aggaaaatga gcagacactc acacacttac tagttgctca
63121 cgctattctt atcttttaag aaagtcccac agacagcttg ctcgccactc ccgtcccccc
63181 aaagcactgg atgacactcc ctgccaatgt tgctctgagt gttctacaaa tatgtaaaac
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63301 ggggttcagg tctacacctc tgaaaatcct gagaattctg ccagattcaa gaactcagtc
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63481 attgaatgat gaaggggttt ggttccagct aagtggtttc cgccccattc ttcagattga
63541 gaggagtcag tggtcagcag ttaagcctat gaactgcagc agtgaccagg atattgagat
63601 gttcctcagt atgtaacact ggcaccttga tctggggaca accaacagct gtctaagtgc
63661 actgaaggcc tgagcactgg gaggaaattc ttgcccgatt ctgtaaacct agctgactct
63721 ctgtagtgtc gtggacacta gagaagaacc tgctactagc acttttctga agcagtgagc
63781 ttctacccac agataactag ctctcaggcc tcgccagaga agcctctttc tgcagcagat
63841 ggaaaggatt agagaaaacc atgactggtc aaaatgcagg gaaccactga ccatggggta
63901 cccatgccca actgatgata gacccacacc acaaccccca caacaaatgc tcatggaaca
63961 ctgcaaaata agtgcgtggt acgattctaa gatccagaag cccagggtgt ctgctgaggg
64021 atgccacctt ttatgtaaga caccacccgc atgcgtgaat cccaacaacg cggttaccta
64081 aacttgcgta atgacaatac cagttcacat gctttgaagt gtggggaatc tctgaagccc
64141 caccctaga tgagaagtta ccagcagtta atggctgctg agagagaagg aggatcagtc
64201 tttatcaggc ataagcttgc tgataggtta gccaatccca cgtggtcatc cctaaacaca
64261 tacatgtacc agtaacacta aatgagcttg gcagagcatg tgtgtatatg tatgtaggtg
64321 tatatgcata tatgtatata gacatatatg tatcaatgtg cgcacaagtt gcttagcaac
64381 aataattaaa gtagtcatgg aactgagaga ggtgggcatg gaagaagctg ggagagggag
```

FIGURE 6Z

64441 gagccagatg gtgtaaatac agtactcatg tcagaagttc taaaaggcta aaactaaaac
64501 aatgaagaag aagcatcagt gaactcttcc aaggccagac tgaaaacgga ttcatgtact
64561 gggaagatga gtgtgtctga ggacacactg ggggcctctg cacactgcca ggtctagagg
64621 agttaaggga acgtaccagt ctcctgtggc atgctatgca tcgctccagt cagacctcag
64681 gaagaaatcc ttttccataa gcaagatcag agaggcgtcc taactttgcc agggttgcac
64741 ggataactga caagttccaa agtcagagcc tggctttcct gcagccctgg ctcagaacag
64801 ccgcaaccca gtaactggga ggctggattc ccgtcatgta ccagaaagaa tcagtaagac
64861 tccagttaat atgggaaaac aaacaaacaa aaatgagtat gcggagaaga agaagcgaag
64921 ggctgtgagc tttcatctga gagcccaacg gaatgcagat cagggaatga aacggaccga
64981 agtgcctcca tgaaagcact ttagatttca ggcttataag gagtctatag caactattgg
65041 acacccaagt tgacatgtct acacaataag gatggcgttg tgggtaaaaa cacttgctat
65101 gttaccctgg caaccagaat tcaatccctg gaacctgaga atcaactctt caatgttgtc
65161 ctctgacctc tgcacatgtg cacaccaagt acacaccaac agtatagaga tgtctccttg
65221 gaaaggagct ggggactcag tggagacatg ttcctggacc gcgagccact caccaatggt
65281 tggtctacct ctaaactcta ttcttaatcc tgaaatacta caaaagccaa aattaagtct
65341 ttttcaaaat cgatgggatt cagcaccttc cagtttctaa aagtactccc acgtgcgcct
65401 ccctgccaga gagaagctcc gagctttcct tttcccctag gagaattcgt ggttttgtgt
65461 tcctgattct acgggtcagg ttgttctgtg ttctttttga gtttcacatt tcaacaggga
65521 cacagaggaa ctggaacaca tccagaagga caaaactgac agaaaattgt ctatgcaact
65581 ggctttcaag aaagggccca aagacctgag aatatttaat cgggagggaa gaagtctgaa
65641 gaggagttta atagaattca cgcaccaaga tttccttaaa aacagcaggt gatgccgagc
65701 tttcaatgtc cccctctgag gattagaccc aagaaaactg tgctaaactg cgtcttgtcg
65761 gacaccggga aaatttccca gaagccaaga gcgctagcac gcagcttcaa tccccctgtg
65821 ggatgtgcca acttccactg gagaaacccc attagaggac ctcttaagag tccccagtgg
65881 cattgcagtc ttagctttac aaaggcagct acaaacatgc cctctcctaa gaaaagccag
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66001 ctccagtgtt ggcttagtag cacgacgtgc tacagataag cggaaatgta ccccaaggca
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66121 ttaggagctg ggttctagag gaagtcaggt cactggaagc aggtgtcctg tgagagaact
66181 gtgaaacccg ggccctttct gcctttgga ggtaaccagc ttggttccat catgtgcttc
66241 ctgcttctga cattttgtct cagaacagcc caaaagtaat agaatcaaca gacagagcac
66301 gacaaccccc gaaactgtgg gggccacccc tctaatcatc tctgggtttt gccacatcgg
66361 agagctacag taacatcaca atggagagtt agcacataag ctaactgatg acgctaggct
66421 acccagaaaa aaatgagaaa attcagagtc tacctgacag aactctcagt ctcatcatct
66481 ctcaatctag acacagtagc agcagataca gggaatccta gcttcctgct tacggttcta
66541 tttacttctg tctttgtgca gtcacgatga ggattttcga atgtcttgcg tatctttgaa
66601 tatctggaac tggctaggtg ggctatcgaa gtgtgaactg acataaagtt atacatgtat
66661 acatatttac cacatacaac atatcttaaa gcatgtgtac attaacccaa tcagcatcag
66721 cattaagtcg cattgttacc atttctgtgg tggtaacact ttcttagcaa tattcaataa
66781 tgctttatta accatagcta gtgtgttata aagctcactc ttctatctac ctaaaattgt

FIGURE 6AA

66841 gtacctttg agcaacaccc cctaagttat gttcccctgg taacctgcaa gactctgagt
66901 tcacccttt agatttattt catatatacg tgagatcacg tggtgtttcc ctttctgcac
66961 cttctattaa cagtattcca ttacatatat ggaccacatt tttacccagg cacctgctgg
67021 aggatacttc attgtttggc tactgtgact agtgggccaa aaaaacaagg ggggtgtaga
67081 tttcaacaca actaacttcc atttcttttg gactgggatt gctggatctg ttgagacctt
67141 gtctgaatca agaatccaga agagaccacg aagaacataa gacattagga aacaacagtt
67201 ccccacaccc tagattctag cctcaaagct gagctgagat tttggggggt ggggagtgca
67261 aaaggaattc acatttgatc ctgtatttgt ttggatatta catgaacacg aaataatcta
67321 aaaaaatttg gcttctcata agacacgtaa aaattcacta tgtattattt caccaaaaag
67381 actcaatttt ttttttttt cggtcaaaca agcatgcagc ccttgcattt aacatttcac
67441 aacatttact tttaaatctg aatcctaaca gctcactcag tggtttctgt gaactgtgaa
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FIGURE 6BB

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FIGURE 6CC

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FIGURE 6DD

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FIGURE 6EE

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FIGURE 6FF

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81001 ctacaggcga acagacatgc tccgctactc aaccggaaca gcttacatac tagcagcaaa
81061 ggctgccatt atccctagga ataaatccta cccatgccca atcagcagtg catgatggga
81121 tgggagacag cctggctctc tgtacatttg cctctcgctg caagaagcct tcatttcagt
81181 ccctgagtac gtgggagagg acagacatcc agtgtctccc tgggctctca catcagggta
```

FIGURE 6GG

81241 gctagatgca gcgtgtaaca tggtggcttt ccacatttag tatgtacaca gcttgttctc
81301 agtatcccct accgctagag cttctggtgc agaggtccag agtgcaccag gaatctcgat
81361 gtctagcagg taatgctgat aaacaccagt cctgggtcca cccagaaact accaggccgg
81421 ccacggcact gtttccaagg cctaacttcc actagagggg agatatgggc atggccaaag
81481 ggaagatagc tatcttaggg ggccaagggg agagcaagga ttctacttgg gtgtctgcat
81541 aagttttttt ttttttttta aacagttatt tctaaatcca cccacagacc agacaaacat
81601 gtcccaaagt cctgttctgc cctaaaggct gtgtccacct aggcaccacc tgctgagagt
81661 cctcacccac attagaacta ctgcctaggg ggtctgcttt caacatgacc ttcacatact
81721 gagaaatgag ttacagctgc agggttgcca agcctctccc gacacttcct ggagaactca
81781 ttagggagct cagaggccag gacccaggac cggaagagcc atgaattccc cacaggacaa
81841 gccacaggca gtttcctcgg tgctatgaag agcagcgttc atgtgcgtag gtgaagtctg
81901 aggtctcgtt ggttttaaga ttccttatga gagccagtga gatggctcat gcgtgcaaga
81961 gtacttacat cacaagtctg gtgatcagga ccccgagaag gaagaacagt tactgtgtaa
82021 ggctgtcctc tgacctctgc acatacatcc ctctcatagg taagagtcct cacatggagg
82081 agtcggagct caagtgtgag ctaagcagtt gaatggaagc cccaaccctc cttgagcact
82141 tctgcgcagg cttcagcgca gggtctgcac acgcacgggc tcaatgagcc gctagccttt
82201 ggtaaggagt gttcccctac catgcttgtt tattggagta ggaaacaaag accctgatca
82261 aaggaatcca gatcgtagta cctaagagtg tatgtcctag ggaggtcctt ggatacctgt
82321 cagtcagaac tgccacctac gggacccacc aatgttcact cttattgata tgggggtggt
82381 caggataggc agacaactga aggataggtg taatggtgga aagattgggt cccattaggt
82441 gtcttgccta accatgggcc attcttaaac tgctgcctca acgctaacct caccggtctg
82501 gctgctccca agtcttgaga gtcccaggag acaaaaatct cctgttattg aagacacctc
82561 caggccggat acaagggcca actaatcagg tcaaactccc atctccatct aggccaaggc
82621 ctcttagtaa actaatttct caagcaggaa acagaattgt actgaaaata ccttccttct
82681 gagccacaca ttcttctccc cagggaggga gcatgaatta gaaaccagga atttgacaaa
82741 tgaatggcag gcacatagaa actcagggta tttgactaat cactttgaaa agcaagatta
82801 tcttttcaca gtaaacacaa actttctctc tttaaacaat gcagagaagg ctgggagcca
82861 gaataccaat atcaataaaa tccaggcatt gtggagccta cagaaggtaa agaaaaataa
82921 aaaccttcac caaaataata atcaacctgc tggggagggc ccgtccacac agtgcctgct
82981 tcccaacccc cacccgaggc ctgcctcctc aacaccttct gcaatagtga gagttaagag
83041 atatccccag gtggagattt gtctacacac cttcaagata ctaatgtcct tgaatggtca
83101 ttgttttctc agggagatga ctagttaagg gaaccactca ataaatgcga cttcataaat
83161 cgtttctaag ctcactgcct ttttacatcc acagaatatt tttaaaaacc aaactgttca
83221 tttttttcc tttggctcct acacgctgta tgatctcccg gagttttatt gagtggtatt
83281 ttggctctta gttcgatcct tccttctttc ctaccttcct ttctgcaccc cccccacccc
83341 ctcaagacag ggtttctctg tgtagccctg gctgtcctgg aacttactct gtagaccagg
83401 ctggcctaga actcagaaat ccacctgcct ctgcctccca agtgctggga ctaaagaaat
83461 gtgccaccac tgcctggtag cttgtagctt tttcaacatt agaaaaaaaa atcccctcta
83521 ttggatgggt ttcacctgcc aatgcataga cctactagga tggttagtca acaatttggg
83581 ggccctgtca catgataagc tcacagccaa cacttagcta tgatctgtgg ctaccatttc

FIGURE 6HH

83641 taggcctccc ttttaagtga agactgcagg ggaccgagtg tagagtcttc catgtaggaa
83701 ctgataacca ggcccaagca ccttctccac tgcttatgaa gtggcacctg aatggtttac
83761 tcagcttctc tagggctgct ggttctcagc tgcccatgga gctatctttt ctggtctctt
83821 cgggccccga ggccaattga gaagaactgg atgctaaata taaaaggacg ttataagctt
83881 tgaatcacct cacaaaggca caggatgacc tgtgctactc tctgaactgt caaaagtccc
83941 ccagaacaaa gtcacagaaa ataggtaagt cctgcacctt gatacaggca gggctgagct
84001 caaggtctcc agcctacaca ggacccctct ttcaagctct tactggcatc ctggaagcac
84061 agacaaccaa taactcatat ccatttttgc aaggagacac tactactgcc tgtgacagct
84121 gtctctagag ggcatcagaa gccagtacac tgaagctgtc accagtacag tcatttataa
84181 cactacttag cccatctgta gaatattggt tcacttcagg tccacagtta taccatctac
84241 aaaggctcag ttagtatgga aatatatacc caggcaaaac taaaccaagc accacataga
84301 ttgacaaaat aggccgtttg ttcctgagtg ctttttaaaa acagctttgc tgaggtacgt
84361 tttaccttct aaaattgttc ccactataaa tatacagctc catgggcttc aataaattta
84421 tacagatggc caatcatctt tcaatcatcc agattcagaa catttatatc aaactgaagc
84481 ccccccccc attcttctcc catccaaggc atttcccctg tctgttcacc caggatgcta
84541 catgtaccat tggctagtat cttactgtgt gttttgcgct tatactgagg aacccctaga
84601 ttatatctaa cgcaccattt tgagaaaata ctatggaaaa tgttgctaag agcattcaca
84661 tgtgatattt gcatacacat gcttccatat ctctaggaac agcctagact tgctaggcaa
84721 agtaactaat tgtatgtatt ttaaaagtcc caagtatgtg ctaaaatgtg gttatgttag
84781 ggtctagttc cagagatgca gggcacatta caaaaccctg agtctgcaaa gggtagagat
84841 gcctaaacag actaagaatt ctaactttat actggccccc ttccagtatt tttgttctgt
84901 tcaagacaat aatctttggc agcacctaag agcttgaact tttcatttat ttgattgctc
84961 ccaaaccaaa gttgtccaaa gcagagcatt tttttttca gataatggaa atattttctc
85021 tcttattcaa ggagaaccac atatccctat ccccagacaa aacttgattt tccttcttaa
85081 tccccccat gacccccaca ctttgctaga gatcaggtag caagcaccac acactctagg
85141 ttaagtgctc tatcactaca ccacaccact acttctgaga aaacccttc ctttctgtgt
85201 ctgtccttga gtacacagac gtgcaggctt ctggacacag gagagagaca ctgggcatcc
85261 tcctgttact ctctacccca ctgtcctgaa acaggctgtc tcacggagtc tggctcaggt
85321 caggcaggtc atctgactag caagttcttg ggatcagtct gtctcagctc accacctgga
85381 gctactcctg ggtgcagcta ggctcagtca cgccgaggat tcaaacacga ggcctcatga
85441 ttgccaagca agtacactta gctagggagt catctctcca actcctatga tcttatctga
85501 agttgggatt ctacagctat gccacactac agagagagtg atggctgaga ccaaagggtc
85561 ctgctgctac ccaagtaccg ttctgtggct gtgcaccctg atgtctgctc tgctgggatt
85621 ctgcttcacc tgtcgtcggc ctggaaatca gtgtacagaa atgtggcctg atgagcatgc
85681 atgacccagg taagcaggcc cagaaagaaa acacaggaac tacacgccag gcaaaacact
85741 tgtgttccca cgggggcta ccgagaaggc caagatcaac tgcagtgctt tcctggatag
85801 ctaaggctga aggatacctt catgggggtg gggggtgggg tgggggaaa tattcctctt
85861 tccatcaaga cagaagtctt cagaatcctc ctgagccgca cggaagcatt tatgccattt
85921 tcagtagcca tacaaaaagc tcaagaaata gattccttca acactgagtt gaggcaagat
85981 tgcttaaaaa taaaataaaa tataaaataa aataaaaact cagaagtggc ctgggactat

FIGURE 6II

```
86041 atacatttga aggatcacag ggatagcgaa gtcatttcta atctttgcca tgtgccaaac
86101 atacacagaa atactcagaa agttactcga gcttatgctg gcaactcccc caccccaagt
86161 tttctgtctg acttggggtg aggtgaacct ggtgaagttc cacagggctc ccctttccct
86221 gtaactgtga tgtatccaca cattctggga aacactgggg ggaggggggag gaggctatca
86281 gtataaacga cagcaccctg aaattaaatg tcagataact ctgctaatac acccctcctc
86341 aaaatctcca gtgcgtccca aggcttacct aaatgataac ctctacatct gcatgcaaca
86401 gtgcctccta taatcctagt actgcctacc tcccccagga gctgaacaca agacaggccc
86461 aaatgtcatt ctgtgctctc tcctcttctg tccctgtgct ttctagtccc ccaaaccctt
86521 ccaggccagc tttgctcaga agcctgtgtg gccttctcca ccagagtctt ccttttggta
86581 cccagagcac cttctgtcct ctcctctggg gctctctgaa gcctgtgctt tgcactacct
86641 gtgttcatct gcttattaca aatctttctc tcctttatta aataagtgag gaagaagtga
86701 accagctgag ccctaatact atacaacgag agacaaaggt gagttgttgc tatgggtggc
86761 ccctcaaagc tttggatttc atcacagtta ccagagaaag ctactactaa agagtctcaa
86821 atgtcctggc cagagatatc cttgaagcaa gaggctctca acctgtgggt ttagattcct
86881 ttgaggtcaa atatcagaca tccttcatat catgcattta cattacaatt cataacagta
86941 gtaaaattac agatatgacg tagcaatgaa tagattatgg ttgggggtca ccactacatg
87001 aggaactgta ttaaagggtg gcagtactgg aaggctgaga aacactgttt tttaacacaa
87061 gtctccaggc ctcacctgcc ctccactccc ttctcaaatg ctaacagcag ggctggcgtc
87121 agctttccag ggaagcttcc ccaataccag aatccttaac aatacttggc tgatatttat
87181 agtagccaga agctggaaac aacctagatg tccctcaaca gaggaatgga tacagaaaat
87241 gtggtacatt tacacaatgg agtactactc agctattaaa aacaatgact tcttgaaatt
87301 tgcaggcaaa tggatggatc tagaaaatat catcctgagt gaggtaactc aagtcacaaa
87361 agaacagata tggtatggac tcactgataa gtgggtacta ggcagaaagc atggaatacc
87421 cacaatacaa ctcatggacc acatgaagct caagaggaag accaaagagt ggatgcttca
87481 tcctacttag aagggagaac aatataatca agggaagtag agggtgggag ggatttggga
87541 agaagaaagg agggggaggg gaaaagaggg tgcagagtca ggtattgaag gagctagagg
87601 agatgtacag agggtcagga aattgaacag aggggatggg gaactggagg tagcaaccac
87661 aaagtcccag atgcgaggaa agcaagagcc tcccaggacc ccatggagat gacattagct
87721 gaaataaccc acaaagggga aggagaacct gtcaagacca tatccagagg ttagactgcc
87781 ccccacccca gttgaaggat ggggcaaccc acccatcttc aaagttttaa ctcagaattg
87841 ctcctgtcta aaggaaatac agggacaaag agtggagcag agactgaagg aaagtccatc
87901 cagagactgt cctacctggg gatccatctc acacgcagac accaaaccca gacactattt
87961 attgctgatg ccaagaagtg cttgctgaca ggagcctgat acagctccct cctgagaggc
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88081 agggacccca atggagaagt tagaggaaga actgaaggag ctgaaggggc cttatctggc
88141 atcaatggga ggggaggccc ttggtcctgt aaaggcttga tgccctagtg tagaggaatg
88201 ctagggcagt gaggtgggac tgggtgggtg ggggagcacc cgcatagaag cagggtaagg
88261 tgggatggga tagagggttt gcagagggga aaccaggaaa aaggataaca tttgaaatgt
88321 aaacaaataa aatactcatt taaaaaaaaa aaagacttgg ctggtacttc atacctaagt
88381 tttgaataat gaaaaaatag gctataaata ttcttggaaa taaaaaccag ccttcaattt
```

FIGURE 6JJ

```
88441 tcagcaacat ctaagtgtat gatactttta gttaaggcat aatgataaga taatcatacc
88501 atgtaataat cctgataaga aataatcaaa gcctcctttt gactttctat gcctatcgct
88561 tgctcagtgt ggaaaaaagg ggtgggggag cttatcctcc agtaactaac agatctgaca
88621 gctactaatc cgccaaggaa aacgtgcttc ccgatgtcag ggagtatagg gcacagatct
88681 actgggggga cataatgaaa cgagatggag ttacagttca ctttaaaatt taatacaagc
88741 aacaatgaat taagggtgac cacggcctca tgtacgggag gccccagaat gattgcgaca
88801 ctctgggcag ggtacctggc acatgcagaa ggattcgcaa ggagaaggag gtttttctga
88861 agcttctctg ctcgcaatgg gaagatggac ggggtgagca gctctgtttc tggctgtatg
88921 taccagggga agacccaggc cagagttggt gtgagaaaaa ctggaggttg taaagaaacc
88981 tcatccagac ataccagcct ggggacaagc cttctccgga tcttcccgtc actgtctttc
89041 taagggccct gattgcttag ttaatacacg tataaaactt caaagcatta acacagagct
89101 acaccagagc cgtagcaaat gtctgaaggg gccagcaagg gcacacaggc cagagtctgg
89161 aaagaagctg tgtgcacatg cagtaagcac cagctttact ctctgctgag aaacccacgg
89221 ctgctttaaa acccagcttg caaagcattt ctgtgcagaa ggcacaaccc ctatcaatac
89281 tccaaatcct gaaagctgat caatacacag acgctgtaag ctaatcaatg tacaagctct
89341 gcaagctgaa atatctctgt aataaaatga actgtccgta ctttgcaatt ctttctgctt
89401 ctctgtttga aaaggagatg gcttgggtgt caggtgctca agtgcttgct gtacaagaga
89461 acccacgtaa catgtgcctg aaatctcagc acttagaaag tggacacagg gacatctctg
89521 aggcttgtca gccagttagt ctacaaactg gtgagctcca cgttcattga gagacatact
89581 caaaagataa gatagagaaa aaagacaccc tgtgtctcct tgaacctcca gagggtgtgc
89641 acaaatatat acatgcatac aaatgcattc tctctctctc tcacacacac acacacacac
89701 acacacacac acacacacac accccagagc acagtaggct gaggcaggtt aagtgtcaga
89761 tgaatcacaa tttccctggg agttaagcac cacaggcagg ctgctgtcac tcctgcagga
89821 aaggttccct gggaatacct tggactgcta gaactcagcg ccctagctta gactcgtgtg
89881 gtggtttgga tgagaaatgt cacccatggg gtcacacatt tgaacgaacg gccccaggag
89941 ttggtgctac ttggggaggc tgtggaacct ctgggaggtg ctgccttgct ggaggaagtg
90001 caccaggagt gggctttggg ggttcagggc cttacctcat ttcctgtctc atgtttgcag
90061 tttgagatgt gagctctaac cttttgtctt gcctgcttat tgccatgcct ctcccaccgt
90121 tacggatgct ccccattata agctcctcct tccctaaggc attttggtca tggtgtctca
90181 tcacggcaac aaaaagtgta actactacga tatgcaaccc ttgatgactg caccttaaga
90241 atgaagacac ccatttgcca aattgttagt atcctgtgac aactccacag gacttagagc
90301 aggaaggtgg gtgaccacct aggcagcagg agcaggccca gggtttcacc ttcattctgc
90361 gtaacaaacc caaggatatt tgaaaagtac actaatcggg gctgggagct ggctcagccc
90421 ctaagggtaa gggcagctgc tgtcaggtgc ctacaacgag tggagttgaa cccccaggag
90481 ccacttgaca aaaggagaga ctgactccca caagttgtat tctgacacac atacacacac
90541 acacacacac acacacacac acacacacac acacacacaa acactattaa gacgcagcac
90601 gccacagttc tgtgaaagga gaatggagtg tttacccttc cagctgctcc tctcctaaga
90661 tgagacgaag gttcttcagg aaggacaagg agaccaaggc atgagaatgg cggatcttca
90721 cgtagccggt caccacctcg atgagcccca tgaagttctc caactccgag gcaatgttat
90781 ctagagaaag aggagtccat gtcaccgagt cttcctctgg tcaggtggcg cactatactc
```

FIGURE 6KK

```
90841 agattcacac acactggtgt ggatgcgaag gggaagcagg tcttgcgtgg gggaattgca
90901 gtgagaaggc tggcatagca ccaaccgtcc ctgtctccac tctccgcaag ccacaccggg
90961 acaaggcctc tgaggcggga aagcagactt ctaggaggct ggctgctgca gttgccaagc
91021 tgattaacag aacgtgaaat cagaaatgcc aggctgctaa ttagccccag ctgacaaatg
91081 gaggcaacat ctcttagata tgctcagtga caggcagtcc tggctccaca gtgccatggc
91141 aggactgggc aaacctgtcc cagcctggta agaatggtct ttgctggacc tggagttcca
91201 tatttaaaga ctccatttag ggctgcagga aaacactcca atatcacagc aatgatgcat
91261 gcaggtagtt gatctatctt tccccaccct ggatcgagac agggtttcat gtatgctaga
91321 cttaagatga ggctgaactc ctgatcttcc tgcttcctct ccctgatccc tattcctggc
91381 ctgcaggcag ttttgttttg ttctctctct ctctctctct ctctctctct ctctctctct
91441 ctctctctaa ataatttctg catctctaag ttttctatcc tgctcataat tacttctgta
91501 accagaaagt tgccaggaaa agttgctaat gtaacaggac cgagagccag tgaatttctt
91561 ttatcgtgct tacccacctt tcacatagca agtaacataa actttggttc atgacaaaat
91621 tctaagacta taataaatta ggtgaatggg atttttatta tatctgattc ttgaaggttg
91681 atttggtgaa agtttctcct atggtttgat ataaagaaga ggacaaaagc cttatactaa
91741 gtctgagcct cacagagtcc cctcacttgc aaaatacata cagtgctagt tgtatgtaag
91801 ggctacaggg aattcaacct gaaaaaaaga gtggctgcgg ctaagcctgt gttttgttcc
91861 ccaagaattg aatctataac ccctgtgtgc aagacaagtg ctctggccgc cctgaactca
91921 ctctgtagac caggctagtc tcgaattcag agatctgcct gcctctgcct cagaagcact
91981 aggatgaaag gtgtcttcac tgtgtagacc aggctagcct cgagttcaga gatctgcctg
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92101 gagttcagag atctgcctgc ctctgcctca gaagcactag gatgaaaggt gtcttcactg
92161 tgtagaccag gctagcctca agttcagaga tctgcctgcc tctgcctcag aagcactagg
92221 atgaaaggtg tcttcactgt ggagaccagg ctagcctcaa attcagagat ctgcctgcct
92281 ctgcctcaga agcactagga tgaaagttgt ctgtcaccac acccagtaag taattcttct
92341 tcatgggctg aatttcccaa tcacattgat ctcccatgac aggaagatat aaaaacagta
92401 aggtttatga attttaaaag gcatgtcttg ggatcaataa actcaaagaa aattaataga
92461 tctggtatga gcaaaactac aatttggtta ttaacataag ggtcagcgtt cttgtgtggg
92521 gaacagggcc ctccattgtg gaagggtaga gaatgggcaa taaaaactaa ggacttgggg
92581 gctcgagaga tggctcagca gttaagagca ctgactgctc ttccaaaggt cctgagttca
92641 aatcacagca actacatggt ggctcacaac tatccataat gagatctgat gccctattct
92701 ggggtgtctg aagacagcta cagtgcactt acatataata aatcaatcaa tcaatcaatc
92761 aatcaatctt aaagaaacaa acaaacaaac agacaaatgc ccaagcctca aaaactcact
92821 accacaaaaa accccataaa gaaaaaaaca aacaaacaaa aatccaaaac catacataca
92881 aaaagaaacc ctaaaccaaa aaaaaaaaaa aaaaaaacaa caaaaaaacc caccttgttt
92941 ctattacctc tacagactaa gaatataatt cacttattta acaaatactt aggggcaagc
93001 aatccactat aaataaagag gacactttgt ctctgaagta aagaaaaact ttctttccct
93061 aaagatttac cagtaaagat taaaataata gtcttctgcc tatagtattt tacctcatga
93121 aactactagt agctcaacct agaagttcta gtggcaggaa ctgaagggca tctatctagg
93181 ggactttctc tgtcagtcca agactagaga agataagatt acagggctct gctgccacca
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FIGURE 6LL

```
93241 tgggagatgt tgttcatgaa tacaattctg aagcaacatc ccaggagcgc tgtctacacc
93301 aagtgaagaa agggagtctg caggctcaga ccacagcttg aggtgtggat ggcacatctt
93361 tctggctctg agaggtaaaa caggagatca ctctttaatc tttcctttgc tcagtctcct
93421 caacggaggc aagcaaccca aactctggcc ttacagaagt gtggactctg cagcagctag
93481 catgagccag ccatgggtct gagccatcag aggtgtgtgt gtgtgtgtgt gagagagagt
93541 gtgagagggt gagtgtgtgt atgtgtgtgt gtgtgagaga gagtgtgaga gtgtgtgtgt
93601 gtgtgagaga gtgtgagaga gagagagaga gagagagaga gagagagaga gagagagaga
93661 gagagagaga gagaacaggc ctttcctgcg taagatgtga cttaaagaaa gacgagggct
93721 gatcctcttt acaggagtat attctgggct aatggctcaa acatcgactg tctttctatc
93781 tggattttat gtttccgaga aactcacagg ggaggcgtca cacaagaggc ttacttacat
93841 cccgtgctgc ttttctaagc ctgtattctg cttgtgacta aagggacaga gccaggaaga
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93961 actgcctctc cggatgttaa taagcagatt gcccttcagg atggtgcatc cttggagcat
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94081 ggggcagggg ccttcgcagg ggatacagta catgctggtg aagataaaga gtggaccaaa
94141 accacaaaag tgagtttatc ttcttgcatt aaaacaaaca aacaaaaaag aaaacaaaac
94201 agaaaagtaa ggaggctttt tgtttgttat tacagcagca tttcatgaaa gaaccaggct
94261 gaaacatcca aacaatcaca cagtataatc tcctacccag ggcaagccat ccaagctgca
94321 aacacacaga gggaacacag actgcagaag aggaaagcat gtcgcttgtt tttagacaga
94381 atacacttcc catgcaagaa gcatgtgggt atcataggct tgtggctggg gagccagctg
94441 gtctacctgg gagacacaga ctcacaggca ctctggggct ctgaataaat ggagctgctc
94501 actgatgaga ccctcgcctg cctgcatgcc agaggaggtt gggcaagctg gcagcgctgg
94561 ggaagggaca gccgcatctt tgtcactaac aggagtctaa ttcccaaagc ccagggagag
94621 attccaacag gtacctggcg cagtgcaggt ccattatttt cttgctaaag cacaagtgaa
94681 tttatatctt gacagtgctt tgcagaaact tgtaaattga tccaaatgtt gttttgctgc
94741 acatacaata aaagccagga acctccgcag ctctctaatg aggtccttgt ccgaatgcta
94801 ccctcagtgc cacacacaac ctggagccag aagcagtggc atgcttcctg cttcctgccc
94861 atcatttagg aaacggcaga gaagatgcta agcctggggc tataccttct gagaccttag
94921 cctgtataca gaataagggc cgagaagctg ggtcgatttc tgaatgagaa aaatgaccca
94981 atcttctgga atgggtggga cagtgttata ttcaaattac tgctcttaaa tgagtccgtg
95041 aaacctcacg aaaagaaaga aaatcagggt aaagcaagag ctgcctttac taaagtcttc
95101 catccgttcc caaaatacta tctatagtct gttttgttta aaaaccttaa tagttctctg
95161 ttatcttcct atttcctatt aggagagtgg ggctgaggtt ttcacaggct cccatgggaa
95221 gtggacctag ctagccaaag tgggggacat ctggcttcct ataataccac atgcaacatg
95281 cttgtggtgt tggaacgaga atggccccat agactcatgc atttgaaggc tcagtcccta
95341 gctaacagaa ctgcttggga aggattagga ggcgtctggt gctgagctct cagttatttc
95401 cttcactcca ccatctggga tcctgccctt tgaaatcaca agccaaatta gacatacttc
95461 tgtatacgca gctaaggtca tgacatttta tcacagcact agagaagaaa ctaagacagc
95521 tctcatttct agcctggaga ggggtttcct tctgaacttt ctttgtgctc tgtttgtgtt
95581 tttctcattt aactacatga cgcataaaac ccagctctct ctaaaaacaa acaaacaaac
```

FIGURE 6MM

95641 aaaaacatac ttggaataac tgcagcttca tacacagacc cgtgcagaca gtacagagca
95701 cccgtgtact ttccacccaa cgctcccaac tgctgctaca tccaacataa cgataacaca
95761 gtgacctggc acgcgtgtca ggttctgtgc atttctccat ctgtctacat agacctgtaa
95821 attccctact gcaatcgagt tcgaggacaa cttcaacaaa gtcctcctgt gtgttgcctg
95881 tttgtagctg ccctctgacc tgccccagac ttcactatcc ctaactcccg gtaactgcca
95941 aggtgtcttc tactgccacc ttgggaaatg ttacagaaag gcagtcatat agcacatggc
96001 ttctgaggct gatgtgcttc ccaatgtaca acacccttga agttaaacct tcctttacct
96061 ctcctggtga tgttctgtgg ggaggcctgc tttcctactt attgtaccag atatctgagt
96121 tgtcctcact tcctggtatt acaaacaaag aggctacaga caagtacatg aaataaacgt
96181 tcagggtcaa catgactatg tttattcttt ccccattttt tttttatcca aataggaaaa
96241 cctggagcca cctcccgctt tgttaaaatg tctaggaatc atttagcaat tgaaaacatg
96301 tctataaggg tgtgttctga ttatagctta agtttcctaa aacccactct tgtatagaca
96361 gagcacaaac agtattttca aaatactttc aagcaagtgc taaataggct tcaaaggcca
96421 gcagagggac agctattatt tcttgatagt attttaattt aaaatgggag agactgtgag
96481 aacgggcagg gagcagcagc ccagtgcttt aagagcacac tggagggaag gagacccaac
96541 tcctatgaag acacagcatc ctcactgtgt gttacaggac agttgaatgc ctttcagtag
96601 ggagaggaaa taaacttgca ggtcaaatat gatatagtga gtttgatggc cagctctccc
96661 tctttttttt ttttaatttt tattaggtat tttcctcatt tacatttcca atgctatctc
96721 aaaagtcccc catacccacc cccccactcc cctattcacc cactcccccc ttttggccct
96781 ggcgttcccc tgtactgggg catataaagt ttgcaagtcc aatgggcctc tctttccagt
96841 gatggccgac taggccatct tttgatacat atgcagctag agtcaagagc tccggggtac
96901 tggttagttc ataatgttgt tccacctata gggttgcaga ccccttaagc tccttgggta
96961 ttttctctag ctcctccatt gggggccctg tgatccatcc aacagctgac tctgagcatc
97021 cacttctgtg tttgctaggc ccctggcata gtctcacaag agaccagctc tccctcttac
97081 cagccagctc tcccttgctg ctcccagccc cagaaggaag gcattgtctg gactgtgggt
97141 aagcaacttc acactgccag acaaaggtct ttggctcaag atgtagaggg gtacatacac
97201 ccctttttcta tgctaaaagt gattatttag atgtaaaggg cctctaaagg cttatctagt
97261 aacagcttag tcaacagctc aacaaggtag ggtttactag aaggcctgtc tgtccttggc
97321 acatgccaaa agcaatggac ccaagagcta aaaccaacct ccccctcct cttcttcatc
97381 ctcctcctcc tcctcttcct cttcttcata aactgatcac cctaagtatt ttgttacagt
97441 aaccgagagt tgactaacag agactgccaa cacatgaata aaaaaatggc agacttattt
97501 ttagtagact gtattataca attctgagtc attgtagtcc ctggcttacc aaatcattta
97561 aaaatatttg atcttttcct ttttactgtg ataatggtgc agaaattaaa caggtaggaa
97621 tttacttttc atcttagtat tatgaaagaa aatgtaatct ttggtttgat ccagcagtca
97681 gcttacagtt agagacatct ccaaatacta tagcagcaat ggaatttctt tttgaagatg
97741 tactgaacat cttttataga gagtgactgt agcaaaacta tacattttat atacttacag
97801 aattgttagc aatgctggag actggaccta ggtccttcta tgtgccagag attggatcta
97861 ggaccttcta caaggtgggg actggatcca gggcatctca caagtgtggg cagtattcag
97921 aacttcctag ttgtattttc agaggctcag aaatgtgtat gtgtgtacag taccggaggc
97981 agggaatgaa ttacaatgga accttccccc aaagtcctct gctctgttca ggggaggaaa

FIGURE 6NN

```
 98041 caacaacctc agacctctga ctgtcctgtg tttccagagt tataaaatcc tgtcttcacg
 98101 aacatcaccc atgacgagtt tgtggaagta cagcttgttc agtcagaaac agctctgctt
 98161 ccacagtgaa gcctcagagt ccaggaagga aaaccagagg ccacaaagat ggtggaaggc
 98221 ttagagaaag gaggttctgg cagaaaacat ggcagatcag actactagtt catgcccaga
 98281 gcccaggctt gcaatgagac atgggagacc tgtttccagg cctcatgaat gctggtgagg
 98341 gttgtcttca ctctctctca gactgagagg caaagctttc actggcctag agtagcaagc
 98401 tgggaaggag tatctgtagt taaagtctcc accgctcatg cttcagcttt gcaggtgcac
 98461 ggggagcaag gctcgggagc acctggccag caagctaatt cttacgctct agtgctagca
 98521 aggcaccctc aaagtttaga aataaaaaag caagctgaaa cagacccacc actccaagat
 98581 tcgcattaaa acaagctcag ccatcaccct ctgacagacc catctgggtg aacccctggg
 98641 aggtcctaca cttaggggct atgcagcaga gaaccctcct gggcctaggg acaagagccg
 98701 ctgacctctg ggtgctgttg cggatgaagc ctgagggaca ctcctgcatg cactcatcgt
 98761 cgtggataac gaagccatcc gagtcactgc tctcagcgtt ggggatgttg gcgcagaaat
 98821 cgcgatccac acagcgccag ccctcgaacc tgtaggtgcc aggcgggcag gcaggcacac
 98881 acacgccttt gtagtagtag tgtctgcagg ccacgcaggt tgtgttgtcg tccggtgtgt
 98941 ggcagctgcc caggcactcc gggtggcagc actcgttgtt ctcggtgcag gctcgcttcc
 99001 cgcacacact tgggcacact gtgaggacag agggagagag ggtggtaagg atgatgggct
 99061 acacagcctc ccctgggtca tccgctgcca ccaccagcgt ggcgtaccgg agactggcta
 99121 gaaaagcaca cctcctctga aatctgcgta gatcttaccg tctgtgaatt ccacttgggt
 99181 aaagacacaa cccaacccaa gtccattctc tcctttagac tcctggtttg ctatgggatg
 99241 agccattaac atttaacacc catggactct tcaaaatgca gtggccacac ccattaaaag
 99301 ggagcccatg gtactggtga acagagagaa atacagacaa tatgggcctc taggactata
 99361 caaggcactg tgctcctcag ctctccttct gtatgagaat tccattctaa gaccccagtg
 99421 gatgcctgaa ccacgcacag aacactggcc tgtgcacacc cccttctccc tcatgcatac
 99481 aaagtgatga agagaggagg cataacaagt acggtggttt gaaggagaaa tgtcctacac
 99541 aggttcatgg atgtgaacac caggccggtg gtggtggtct gtttgggaag gttacagagc
 99601 ctttagcagg gagctggagg aagtcctttg ctgggggtag agtttgtttg gggttttaca
 99661 gcctggccca cttctctatt tcctgtgtgt gggtggaatg cgatcacttt gtgtttcctg
 99721 cctgacaaga ctaaagccat tccttccccc ctccccccgg ccaccacaag gactctgtcc
 99781 cctctaggac tgtacaccaa gataaacctc tatctctggc tccatttttc tgtcaaggta
 99841 ttttatcaca gcaacaggaa agttccaaat aaaacaggga actagtcaaa acctctaggt
 99901 tactgcagca aatgttaacc atacccttta caaaagcact gcgtgactgt ggcctctctc
 99961 ttctcaaact ccagaaaaag aaatccaggc tacggaggga ctactctttg ccatgggcac
100021 agaagtaatt atggtctcta aagaggaaca agctacaatc gaagtgccca gtgcttatag
100081 aaggtctttg gtaatgcccg catctgcaac gtctcttcac aacacaacct tcagatcaca
100141 agcaagctgc tggacggtac aggatggtag tacacagggt ttctgtaccc aggggccacc
100201 tgctataagc cttgttaagt taaaggccag gtccagtaat cacagatcta aaatcacacc
100261 ctgaacaggt actctgctat gcacttctgt aaatatgtca tgatgaacac acgcctatga
100321 tccttacttg tgaacaacat ataaaacaaa caaacaaaca aacaaacaaa caaatctggc
100381 taacagtaca tgtacccaat tgggggaagg gattgtttgg aaatactaca gaactacata
```

FIGURE 600

```
100441 aatatgtata ttttaactgt gatgtaccaa agagtcaaga ttccatgttt tattaaaaaa
100501 aaaaaaaact actctaaaac caaaactaag ccaaataagc cccagtaacc acaggttaac
100561 ataaagaaca cacaagttca tctgcaccca aaacagccgc tttgtcaacc cttcatgacg
100621 tggtctttcc cgggttcttc ctgtgcacag gtgtatgact acacatacct gaatgttaaa
100681 ccttggacta cggagaaagc actggataga cttggagtgg ataccaccat acagcaatct
100741 cgctacgtct caccgttaca gctgtgcccc agcatcaaac gcgccctcca tgcccacaca
100801 ttactgttcc atgagtacgg ccatctttgt gggcacctct gcacgccact gggatcagtt
100861 ttcagaactg actgcacgga gtcagtatgt gctctggagc cttacaccag tctgtctaca
100921 cagctctaag tcacatccaa gaattcctgt gtcactgccc ttaaaaacag ttaaatcagc
100981 agcatgaccc agtaaggaga ccggagttct cgtgacactg ccaaatcgac ataatcttgc
101041 atttgactct aaagtcatcc ctccacagaa acatcggggc atttcccctc cctggttatc
101101 tccccctgta ggagttttag gtgttctgct gggtatgctc tttggctcca aggcctccta
101161 gcctccactg tggctagagc gtggctgctc tgtgtttgaa gttcgttcat cccatgggct
101221 ataaagcaaa agttttacta gagcttcctg gaacactcct ttaaaaatac agtgtgtgtc
101281 tccttttttc ttgctggctg aaacatagaa atgatgcaca gatattcacg cagccatctc
101341 agatggaaca tgaggcaaca tagtgagttc aacttggcct ctcaagatgg ctggtgtctc
101401 tagaccagtg gttctcagcc tgtgggtcgt gatcctcttg aggggtgaca tatcagacac
101461 catgggtatc agatacgtac attatgattc ataatagtac caaagttata attatgaagt
101521 agcaacaaaa taattttatg gttggggtca ccacaacata aggaactgta ttaaatagtc
101581 acagcatgaa gaaggctgaa accactgctc tagactaaca ctgcagctgc tgacctttga
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101701 acctatcttc agagccacac acaagtgaag acggaaagcc ttctcagctg gtttatgacc
101761 ttcatttatt ataactagct tcaggctgtt tttggacacc cattctagct caggaacaag
101821 cagaagttaa ttatctctgg tcacaccaaa aaacaaacaa acaaacaaac aaaaaacata
101881 aaacaacaac aaaaacacca aaaatcaaac caaacaaaca aaaacctgca ggagccccta
101941 atatcagaat tcagacactg tctaccacag caattacctc aaagacagta aaatggagtt
102001 cactgattta acagcctacc atgtttttag cttcacacac taccactgat tctttttca
102061 ctcaaacaca tcaatatatg acacagttga agatgatagt ctgatgactt aattaaacat
102121 atgcactgca cgggttacat caaggtttgg ggtctaaatg agcactgaag ttatttgtgt
102181 taatttttt ttttttaaat ctgtcaatga cagaagtcaa cgatctgttg gcatttacgt
102241 acccacccag aatttactgg ataaacgctg cacctgtgtg ccaggcaact ggacatcctg
102301 tacaattgta cggtggcagt ccctgacctc aaggaaagga taccacacca gggaagcagg
102361 aaagaccacg cacagggtgt tcctagtact gtgggttcct ggaagggtct tcagagacag
102421 tgagattggc actgaaaaag gaaggccgat ggggaggggc atcaggacca cccgtcacag
102481 aggtcctcag atgtaaatac aggctgagat gttgctggaa acaaaatgga ccagctcagg
102541 gaggtaccac aggcacaccg attgacggac agcaggaaat caccctgctt taggcaaggg
102601 ttaggttctc acactagaaa ggtcagcatg ctgtatagcg aaggcatgat aaccagagtg
102661 ggcagaaggg cagaagaaca gccagaggag aggaatctgc tactgattac actgtccatc
102721 tatggctcac acagatacat aaagttcaat gtaactcgct aaaggctccc tggtgcagct
102781 gtcccagcca tccgccaaca ccattgctct gtgattcgtt agctcgacgt tatcagcaga
```

FIGURE 6PP

```
102841 gattatcaat gaggactaga tgccaacttt ggagcccttt acttacttac ataggaaaga
102901 aaatgataca tcacaataga tgatgaagtc aaatagctac atagtagtca aagcccatac
102961 catataaaag caggggaaa taaccttgta cactgtcttg aatcagttac cccccaaatg
103021 caaatgctac atctttccag gatgagaaag agaaatagaa atccttgaca aaggatttgc
103081 taaatttgag acatgttgag ccctgttcca ggcctgtgat gggaacttct tctcaactaa
103141 gaaccataaa gttaaaaaca ctgtctttac agatagaacg gttcttttaa ggcatatacc
103201 agatccatga gtcccttaac actcagtgat gccaactgtg aacaaatgcg catctgatat
103261 tctgtgggtg gaagaggaca aaaaaggggt atgcagagag ggagagagaa gatggaggaa
103321 ggccgacctg cttgctaggg gactgactct agagatctgt gtgtggctac agggaggaaa
103381 ggggtgtggc tctctctcca gcacagagga ttccaggagg aagcaggaga acgcagggct
103441 gggattagac agtcctggag ccagcttcag aagcctgctg taaattttgt ctcatctcga
103501 tgtatataaa tattattagt gttcaggact attaagggat ttcttgaaaa gccccgggca
103561 gtgcgtctcg ccagcagatg gatggctgct ctccatgagt gccaaaactt aaaatttagt
103621 gcagtaacca aatttccaat tacagcacca tgggggggaaa ggaggggacc tcccccgcca
103681 ctccagagga ggggcacaca ggcatggtta aagggcagtc caaccttaaa aagaggaaac
103741 ggaagctgtg aactagggca cgaaggaaag caaattgatt ttgcccatga gaccgttcta
103801 ttccttgcca ttaatcagcg aagacaataa aaacaaaacc ttattgaaac agtcagaaaa
103861 gctacaacat gtcctgtgtc agccatcaga aggacaggtc cagggtcagc gtgcatacgg
103921 aggccacacg ttttaaaact cctcttcatt tctttaagag aggacaaaca agcctcgcac
103981 atcagcttgg tccttgcatt tagtaagttc tttctaattt ccctttagcc cgtgattgct
104041 tctgtcagtg aatcctttca tgatcgaaag ctccgagaag cgagcaagct aaagcttccg
104101 agtccaacgt gggaagaaga agtaacgaga ccgcagaaga gaaggatgga agcattagac
104161 aaggcagtgg aaaacactgg tgggaacaca gaggccagtg agggaagggg gaggtaacag
104221 gtgctctggg tgactgtcag agcccatggg gagtaaggtt ccgaacatcg tattcaactg
104281 tagtccaaac tctagaacag agttaaaaag ccatttgcta tcagtccgta agtctctctg
104341 gcaagaatct tcatattatt tgaaacacca cacctaggat ttccatgggc ttccccagtt
104401 cgaaactaag ccaacaagac ctgtcttcag gctctagtgg cctacctcca aaggaacctt
104461 tctcatttca ttaacccaac caagcactct atggaggagt gtgtggataa gccttgaaat
104521 agactcgtgg ctaatcttgg gagcatcctg cccagtactt aaacatgcag aagcctcctc
104581 cgtcctgccc ctcctcttct ttttctttcc tcctcctcct cctgtttctc ctgctcctgc
104641 tcctcctcct gctcctgctc ctcctcctcc tcctgctcct cctcctcctg ctcctcctcc
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104761 ccaaggcaag aggacatgta atactcaggg ccgtcacatg tatttgttta taaagattta
104821 tacattctac tttatgtgtg tgtgtatgta ccacttttac gtctggtacc cagaggttag
104881 aagaggatgt cagatttctg ggaaactgga gttacagatg attgtgaaac attatgtttg
104941 cgctgggaac ctaacctggg tcccctgtaa gagcaacacg tgtgaataac cactgagcca
105001 cctccccggt ttcctgataa tgtacttgta agactttcca gacacaacca tggtaccagg
105061 agcccaaggg cagagtatca ccaaggctgg ccatgccttc tgttttgtcc tcaggttaac
105121 cagcaaggag gatgctcatg atgctcccat gccttgctac ctttcaggaa aggcaaagat
105181 aggccaggga actcaggact cctcatagtt tggatggaag ttccagtttt caaagaatga
```

FIGURE 6QQ

105241 gtatctctgt tggcaggaac tgtgcctgac tgaggaggag caggggacca atggcaagaa
105301 caaggagaaa aagcccagct gggggtctgt gctgtgtcca ccttacaagc atcacaatgc
105361 tttcagttta ttagtcttca atgtaccccc ccactatctc tcttcacata cctttcccca
105421 ctccaatctc ctcatataaa ggtactacta tgacttcact gtacctctga aacaaaaatt
105481 acatgttgca atttgactat tgtcattatg gtgtggtggt aagactaact aaatctaacc
105541 aaaccaaatc taatctatgt tggaggtaag gcctttggga gagaattagg attgtatggt
105601 gtcactaggg tgggacatca ttgtggtagt agtgccttta tcttatatat agagagagac
105661 agagacagag acagacagag caagcaggca agctcagcaa gtcatgcctt ggccatgcca
105721 taatgcaata ggaatgccct ccttagagac tgacactaca tccttggact tctctgtctc
105781 cagaactatg aaaaagtatt ttctttataa actaaccagc atcaggtaag ataagtatac
105841 ctcataagga atagatggtg agtgttgctt cttggactca gtcagtcact gggttacatc
105901 ctagcaaaat ctgtggctca actcacaaag tcaaactaaa tagtgcttct ccccccccgcc
105961 ccccccccccc agggggaggg atcgagggtg ggagagtcag agacagagta agaatgagga
106021 gaaaggagaa tgctttctcc aaaaggaaga caaggaccta aaacatactt atggtctttg
106081 caacgtcaaa aggagaactc tactgcctca ctactgagca agcatccaga gttttaaaaca
106141 gtgtctaagc atgtctgcct ggaagactgt agccactgca tagtctgtca cacagcaaag
106201 gcaacttcac gtggcaaaca gtgtcttaaa agcccaggcc gaaaaatcac attggtaaaa
106261 gtattctctg cctaatgcca aaaaccaaac caaaccacac cataccaaac caatccgaac
106321 caaacgaaag caatctcctt ttgtggcggg gcggtaggca gatccagagg agacgtcatt
106381 ttaagccaga atccaaagct atttcagttt ctgtttgaac agaaaggctg ttacagatgg
106441 agaacttcca cagagaaaag cggaccctga gcagaacact cctggagcac agcaagctgg
106501 acagagagag gacaggaccg cgtgcttttt tgacctgttg gcacgctagt catgagagct
106561 cctaactttt ccagcagctg atgctgtaag tcattttctc cttattgact ttcaaaggat
106621 tttcaactgc tctgggttag cttgcttcct aagaagagcc ctgaacagtg cacccgcact
106681 tgggcagttt cttgattctt ggggagtata taaagggcta taagtcacat attgttgctc
106741 ccctttggct ttgccctttg ctttccacac cttgaaagtt gcagggctgc tctgcaggca
106801 gcatggtcca gtcacagacg gccagagtca caggcaggtc cccatcttaa ttccaaatac
106861 atctgcaaaa cccctagaca gtcttccaag cagcccaagg gaagcccact gtttgcaggc
106921 ggtgcccctc aatgcggaga cagcactcat ttggatctgg tttcccaggt gaccttccgg
106981 cagcattcac tcctcagggc tccatgaagg tctggcacat gcggggcaag gctgctctct
107041 cccacatgct tgcaacccta ttctaacagc acaggatcat ttgaatcagt gtggaatatg
107101 ctgagactga aagatgtggt ctgccacggc tagggtaact tgctcagact cagatctcaa
107161 aagtaaggac atgcccacac tctgcaggct cattctgagc ctctaatcac tgagatctcc
107221 caggtcagcc tttccacaat agctgtctga gtctctctta tataaatcca atttatacca
107281 caaaggcaaa atacaaggct gcttattaat acggagttaa ctttcagtgt tatttcccat
107341 atgcctgatg acactttagg tgtgttactt atatgcatta tttaatcctc ctgataatca
107401 caaagggtag gcatccttca cttagagatg gacaaactgg agacatcgga gagattaaag
107461 aactcatgca agaggatcag gctgctgtgc cgttgttggg tgtcacactc agagtcccca
107521 acagatgaca gcagcctctc cacacatctt cccatcgtgg tgtggacggc ttctgagcct
107581 ctctgctgtc tgaaaggcat gctgcagggg agttgcttgc atgctagttt tctttttaag

FIGURE 6RR

```
107641 catgcaacca taaggaagaa ataaaccaaa agccctacta ccctttcta ctctcttgag
107701 gtatatccct aaatctagag gacaaaacaa agtaacatac acaccgaaga gccccgcctc
107761 gtgcatacaa gtgatactag agaaataata tgtatcaact cagtgtcctc tattgagttg
107821 tagccaatgg aagtctcatg gacatttttc tgccacaaat ttaaaagact agatttttt
107881 tttttttcat gagacagggt ttctctgtat agccttggtt gttttggaac tcgatccaca
107941 gaccaggctg gccttgaact tagggatcca cctgcctcca ttttcagagt gttatgatta
108001 aagatgtgga ccaccctgcc tggccgccag gctggatctt gttggtatct ctaagagcca
108061 ctgcaaagtt gcacactaac agagaagctt ctcttctgaa agatgcacag tcaacatggc
108121 ttacctgata ggaaatgact gtgacatcag accaaccaga ccaacaagac ccaaaagact
108181 acaggctcct cagagtcagc tcggaccaaa taagtcgact gaatgcagta agcatgctta
108241 ggttttcaaa tgccctgaga caatactctg agaggtgatc atagcatcct tccaggaacc
108301 ttgctaggtc acaactcatg cctcactcaa gagctgctcc ttcccaagct tgtaaaccca
108361 ctctaacagc acagaggcat tctctttagc aagccataca gttctgtaag atggaaactt
108421 tgtcgtggaa gaaaatctga gtcagggcca gttgagatgg ctcagtgggt agataaaaca
108481 gctatccttc tgatggcctg ttcgaccccc acccccctca ccctggaagt cacatggagg
108541 agggacagaa tcaattccta ccaagtgttt tctgactgcc acatacatgc tgtggtgtag
108601 gtaggagtct cctcccccaa taatgtttct aagttgggga acagttcagt gcgtcctcct
108661 tttgggagag cacagtttga aggctcggag aaaataaccg agtagcatcg cacagtccag
108721 gacagaaggt aagccacaga gttcagctgc tgaagcatct gggaacattt cattaatgag
108781 caaaagaaac aatcgcctac tgacaatgcc tgtgggatca ctgaggcctc gggaaccaag
108841 cagtgctggg cagagtactg agaaaacagg aaaacaaaca ctgcaaaagg ggtaacaaag
108901 aagcctgcgg agggaagtta taaatagcaa cattataact agaaagctgc gtggaaagag
108961 tgaggaccga ggtgcagctg acccaaagag ggagagcagg aaatttcaat aaatgacaaa
109021 ggccggcaga acagagaggg ctctgcccac ggtgggctaa gagtttcctt tcttcttcct
109081 gcacattttg taatatcagc tttacaaaca cacacacaca cacacacaca cacacactta
109141 aaaaagcaga aagtctggtg gttttcagtg tcttcgtaga gttgtgcaaa tactgccaca
109201 atcgacgtta gaatattttc atcatcccaa agcaaaaagc ccatacatag caaagcttcc
109261 cccagctctg gggaatgact aatcttactc gtctccactt ctccactgaa tcgcctgcca
109321 ggagcatttt acttagtgga atcaaacaaa gggtgttctc ctgtagccac tgtcttccat
109381 ttaaaacaat gctttcaata ttcacccttg gcatggtgtc tactagtcct tctggctttg
109441 ggctgtactg attctcactg tgggaaagcg agcctttcta ttaatgtgga gtgataacat
109501 cgtaggtatt gggagtagaa atgctagaaa cactgacaaa ctcggaaggg gtaaggatgt
109561 caaaggatgg tggatgctga ggtccaggca aggtgctgag aagggtctgt ttgcatccca
109621 gactctgtat ttttggctaa ctctatccac taacttgggc cattctttga tagacagggc
109681 tgtcacagtg ggcataatct gtagaggaat tgtcacctac agtgtggact gtgtctcccc
109741 tctgctcagc aagctacctg tgccacttat ggaaaaccaa gtgcacacac atgagcttga
109801 gctctgtaga aatgcctgac aaatggatgg ctgaagctgc aacactgaag ctctgctaag
109861 atggggagag agaaaaggaa gggcaggaga gagtcaatgg aaaagatggt gacgaagggt
109921 gcagctcaac cttagagtcc ttttaccagc actatattgt tctcacagac tgtcttaatt
109981 cccgtgtact tttaaatagt cgaaaacgcg attttcaacc tattttaaaa cccacataca
```

FIGURE 6SS

```
110041 aatttgaaaa actgcaggca gattttaaca caggggagaa aacaaacaaa gagagctggc
110101 atgggggtca ggacagacag ggccctcaag ctgatggggc atggtcagca ggggagggca
110161 gcttcatggc tgcttcaagg atggagaatc tctgtctcac aaaagtcaca cactttgtcc
110221 tcaagagttc tgaaaaaagg aaaagaagca agaagtccct gcagagggcc gactcccctg
110281 cagccgttct cagcaggctt gagcacataa agatcacttg tgactgcctg tcacagatgc
110341 tcaaatggac aggatgggga aaaaaaatac ccttcacaca cttaaaaatt actctaagtt
110401 attttaaatc tggaactgtt tgtatattcc ttataagttt atgaaactca cacggtcgct
110461 ccatgactaa ctgaagcgga attgagagag tagtctctat ttataacttc tctgcttgtg
110521 cgtgcgtcca gccctatttc cattctctgg tactgtacgc agagttatgt gaagccgtgt
110581 gggctctgaa atgctactta cttcctaaca aggcaggcct gtgttccata ggggcaaatc
110641 agtgggagac ggggtgaggg gttgcaatga ccaagtgaag gccaggctca gaggggaggt
110701 ctcaagcacc catcattgct caggcagatc ttttgctgtt ggttttgttt gtttgcttta
110761 ttttatttat ttatttaaa gacagagttg ctttgtaaac cctggctgtc ctgggacttc
110821 ctctgtagac caggctagcc tcaaattcac agagatccat ttgcctctct gcctaccgag
110881 tgtttatacc acctccaccc ggctagactg cacctctcta aacgggtgtt tgagcctgtt
110941 ttgggacaat cgcacacctg gtgatggctg agagatctgt tctgatggtg tgaattcatc
111001 aatacacaca ttcccaggtc agtgccttaa atctgtgtgc ccgctcatgt cacctcttcc
111061 acttgatttt agtggaattg tgtcaccaaa gggtgcaagg ctttaacagg tcatgcataa
111121 gcctctctcc atacacaaat gtttatgtga agataactga aatgactgac cagagtcacc
111181 catgggacaa ctagtactca gagcagagca catgaggcct aggattaagt tctgttacga
111241 aaagcaagac ggttcatgga gagagtaata aatgtgaaag atacacgcgc acatagacta
111301 cccatggaat tcggatggct acatgtacat ggacacgaat cccctattca cagctgctcc
111361 catcaactgt aagaacagct gctctaaggc tgcctagtca tagtttggaa gaaaaaaatc
111421 aaaaccaact cctggaatct tctctaaaac aatgctctgg tgactgtagt tgtctcgctt
111481 catgctgctc caagaggagg aactccccat gaaaaggagg aaaaggcagt ccacagtcca
111541 cgcttccttt ttgggaaaga tcagaagggg taacaggcac ctcacacctc aatcctgtga
111601 ctaattatga aggtggttta tttttactgc atagcctttt cttttccagt ttatatcacc
111661 tcttaatgtc tccagattca ttcctttcta gaatcttaaa cttcattaca gccatctctt
111721 atgtccatgt atgaaataaa ttaccactaa aaacatccct gagaaacatg tctaaggcaa
111781 ctcagtcact gtatgcacac agtgaagttt acaggaacta ggaggactgt gacatcatta
111841 tagccccgac ctgaacagga tcactgatgt gactgaacct ccaggatgca cagctgcgtt
111901 taaatcagtc gcagttcttg aagaagcacg cactttctaa acacagcacg gatatcaaca
111961 gctggtcaag tgaccttcag cctgctcctc tgaggcccct gcctctctgc tcaccacttc
112021 cttcatcctg ctgctctgct cctgtaactt ggctggaaac atgacttagg tattcccagg
112081 accatcctac tacatacttt tacttaccaa gtagcaatca ttaaaaaaaa aaaaaaagct
112141 cagctagacc tttaaattat ctaggagggt agaaaagcat tgtccctgat aattgtacat
112201 cctgaaaaat actatcacta gcataaatac atggaatatt cataatcagc ctatctcact
112261 gttaaaaagt acctagaaaa gagaccatgc aactgttgag ataccatttc tagaatctct
112321 ctctttttct gagtgtgcat gtgcgcacac acagacttct gttggctttc attgtacttt
112381 gcttgaattt tgtgagcaga gggggtggaa aaaggtacca acttggctaa aacgcatcgc
```

FIGURE 6TT

```
112441 aagtgttgat gccccatagt gccaatagga atccgagtat tctggaaatg atcacttctc
112501 agtttcaacc aggtttttc gttttgtttt taaaaatggt actgcccacc gttaaaaagt
112561 tcactgaagg cattcaaagt tcgagatgcc acgctctttt ttaaaaccat tttttaaaac
112621 gattaatagt tgagcactta ggtgggcagc ggtggcatgc acctacaatt gcagcacttg
112681 ggaggcagag gcaggtggat ctatgtgagc ttgaggccag cctagtctac agatcaagtt
112741 ccaggacaga ggtacataga gaaaaataaa caaacacaaa aataaaacca aaatcaaaac
112801 caccacaaca acaactacaa aattgggtcc agactgggag ccatcctagg cacagtgggt
112861 agaacgcacg ccagctgact gaacagttcg gatgaagatg ccaacagaga gaggcccctt
112921 ctgttttttc caattaatta ggaactgtat gtctgtaaat ttttatttgg tctttgaact
112981 attatctcct gatctcagat aatctggttt actctaaggt gctgtccaaa tcatcaagtg
113041 ttccttgatt gctcagacct atccattatc acccttggat gtaagagact gaagcaatga
113101 gaagcatcct ggacctctga agacgagggt gaacccaggg tatcctttca gacactgtgt
113161 acagggcacc tgcatagtcc tgtgatgtca cctgacccca cggggctggg agcagggaag
113221 gtcatacaga gggagggaga tacaggtagc tttctgcttc cttcccgttt gaacctttag
113281 cccaggtctc ccttcatcac ctccagacat gttctggaat accctctagg ctggttttct
113341 acggttcacg ggaattttca ttggaagctg aaggaattaa caggtagatt aactatctct
113401 ataaacctga accccagtaa gcagacagtg ccagcccgta aagcatagat gagtctggaa
113461 cttggaatgg tgttcaagaa tcactttatc cgtggtataa aaatggaagc attcagaaat
113521 gggaaagggc caaactgcac tccgcctcct acaacgggac ctgtgacccc acagaagttt
113581 ggcaatgtca aggacacgcg aagtttagtt gctacacaaa gggactggtg cctatacagc
113641 gatgcctaag atacaggacc atattttcca aatcaactta aatgtgcagg tgtgtgtgtg
113701 cacatgtagt gcacgtggaa gacaaaaggg caatgcagta tgctttccac tattgctctc
113761 tgcctggtct tgtgaagcag gggctctcac tgaagcagga gcttactgac tggccaagct
113821 ggtaaccagc aggccttttc tgtttcctaa ggccacttag tttttacacg gatgccgggg
113881 atctgaactc agcttctcac acttgcagaa ccatctctcc attcctccaa atcaactttt
113941 aagcagagaa gccttaaatg ctgcgaactc ccaaactatc agagtcttcc tcttctaaga
114001 aagtatcccc aggttttcca aattctggac tcagtctgaa agcgagggtc tgaaaaagcc
114061 agagtcatct cttccactcg ggggtgaggt ggaggtgggg gcaataagca ctgtagcaac
114121 ttccttgaca ttcatgtcaa aggagctgct gccttttcttc agaccccaga gtttcctcat
114181 ccagcaggag gaggcaggga ggtcagggtg cagaagccgt ggagcctgta tcctagtctg
114241 cagcgtatgt caaggtgtgc tttgtcccga tttagagaca gagcgagcgt tgaagtgaaa
114301 aagggttaag aggatggaac aaacagaaca tactttgcag gcaatgacag tgacccaggt
114361 aaaggcagaa gctgtgctca actccctgta atgggagcca gacatgcaac ttctgttatg
114421 caatgctttg tgaaaagggg aaggcttttg gtggtctcca ctctcccacg ggggcctctc
114481 tcccacggcc taggaacgca ggagagagga ggaatggcca ccacaagtct gggctgcatt
114541 cctctgttct gcttctccat ggggcctggg agcgagcacc tttgcaagag aaaactcccc
114601 aagagctact ggattctgga gcaaaggcaa ctcaggaact atgaacccag aggacggaca
114661 tcttcacttg gcagatggag aaagtgaagt tcaagcaatc taagcgagga aggttgtagt
114721 gctcgctcac tcactggagg ggggttgggg ggagcttgtt caagcttcca aggagtgaac
114781 acagggattg ggacaccaga aaagcagctt ttcttcatct ttgaaatcac aagccctttg
```

FIGURE 6UU

```
114841 aacacacgaa ccgcacacct tccttaaaga aatactgggg attttgaaat caatttaagc
114901 acctctaatt tccaaccctg aaacgtttta ctacgtgcat tctctaactg cactcgtctc
114961 tcaccttgta aacaagcaag atcggctgga tgagtgtccc ctaattacgg tttccttggt
115021 gcccgtctat ccgcattggc agcacctgaa ctttctcctg cactgtatct tcctaaattg
115081 acattctcag cccacactgg cacgctggcc tggtgccatt caacagcaca aatgacacat
115141 cccaagcctg atacttccgt cctcctgccc tctccacact gcgtgtccgt aatcctgccc
115201 tccacccact ccccaaccct ttgaaatttc taaaccccag cagaggaagc cctgtagggc
115261 tcttaataag ctcagtcatg ctcgaaatat ccgttttacc cacagggtat tgtaggcagc
115321 aattccgacc agagcacatc tcggcacgag atcatggcct ccaaagccca gcgttcagaa
115381 ctcctaagag caccgctctc atgcagtccc actggaacac ttgggaactt caaacagttt
115441 gggggtggga aaaaaacatc ctctctgata cttccacctt ccacctacac tgtgggttag
115501 gaaactcctt cctgttgctg tggccacgga gggtacatat cgcaactctc ctggctctag
115561 tgtttgtgaa acccacagga actctgccac cacctacaca gaaagtccca tgccagagac
115621 aacgacgcat aaacatttta tgttaagtta gccacatgct aagaaaatat catcttgatc
115681 aggtattttt ctagttctgt ctcacgttca agtctcaagg cccacgtgga ggggagcacg
115741 gaagtacact ggttgcatat cttctgcccc actggaagat gcttgggatt tctgaagaaa
115801 ccacctgtaa atcagtctat cccttaggta atcgagaaag agagtccatg aattgtgttt
115861 cattgatgtg agtcctatag gtgcttcccc ttggacaagg ataggtacca agaacaccat
115921 cctgggctgg ggagatggct cagtaggtaa agtgcctggt gttccacaaa catagggcct
115981 gcgtttggtt tcctagcagc caaataaagc acaggacttg gcaacaggac cctgggatct
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116101 agataatagt gataatcaag gtggagatgg ctagaggatg atggtcgaca cccaccgtca
116161 actgtggcct tcacctgtgc acatgcacac acaggcagca agtgcacccc atatactaca
116221 cacacaggca gaaagtgcac cccatatact acacatacag gcagaaagcg caccccatat
116281 actacacaca taggcagcaa gtgcacccca tatactacac acacaggcag caagcgcacc
116341 ccatatacta cacacacagg cagcaagcac accccatata ctacacacat aggcagcaag
116401 cgcacccaca tatacatata cacagttttt gaaaaaaaaa aaaaagctca aatcaattta
116461 taaaacatta agttttaagt tggcccttaa ctcactaata ttatttgaga ggatcatcag
116521 tgaaattaga aacagaaaga atttaattgg aacctgttga tgtgtttcag gttattcaat
116581 aacaaaaaca atctgccagc ccggtaacat ggtcatttgc tttgaatggg attgcttcat
116641 tctgtggatc cacattccct gaggtgggcc ctgaatggct aggctcatct tctgggaaga
116701 gggacacaat ggcacggggt agcattcctc tgcacattaa tcatgccaaa tatcattaaa
116761 aaacaaaaca aaacaaaaaa ccaaaaccta ccagcccgga agccatggtg gcagcagtta
116821 aagcaacaac ttaagaacag acgaggccca tctgcatgcc gctgtggcca catttgaaaa
116881 ggcccaagga atgtctgtct gtctgtcttc tctgcctaca gttttcaaaa ttggtttcgg
116941 ggagagtgag gttcatgctc tgtgttagaa acatattacc gagcagctgt ctggttacag
117001 aagaacacgg gcttgggaga agttcacagt ccagccctgt cagctgctgt aagtcaaagg
117061 gactctgcct cctcagagtt ccaccggagg cagatgacag acaccacccc gcactgttag
117121 cccatgaaca cacgcagcaa ggcacacagc gacagcaagt gtctcctgca catcggcagt
117181 gctctgtcaa tatcagctgc tgtctccacg taagtctctg gactggattc tcaccttggc
```

FIGURE 6VV

```
117241 tttgccaact atgtaacagt gcaactaact ggtgcacagg tatagaagag atgaggaggc
117301 tcctaggacc ttccgccacg gcacgcttgg aaaaggaacg tgacgaagag cttctagtta
117361 gttcccttca tgtgctgaag agctgcagat ctggtttcat ggaaggatgg ttagatgaat
117421 aagaaagaaa aagagaacta aagaatgttt tcaattttaa aaattatgtg aaattgtgtg
117481 tgtgtgcgtg tgtgtgtgtg tgtgtgtatg catgtgtgca caggccaagg tgtacacatg
117541 aagggcagag gtgtgtgtga gagtatgtgt gtgtgtgtgt gtgtgtgtgt gtgcacaggc
117601 catggtatac cagtgaaagg cagagggtaa gtgtgggagt cactttctct agcctttacc
117661 tgctaagcct cttactggcc cgtaagggca ggaatctgaa gtacttaaac ctcacttctg
117721 atcaaataaa acttttataa actttaaaag accgttttct taatttcagt actcttctca
117781 gacccttctg tcctagagta acctctgtgt gatccacaat agacctgggc tcacccagaa
117841 ctccctgaag gttcaatggt gatggtggtt tggttttgtg cagttctagg aatgtacaga
117901 gacacaggct gaccactgag gtcatgtggg gattaacact tcatcaggta caggagctgt
117961 agctcagggg cagtgtgctt gcctagcatg cttgcagccc tggttccaac ccccaggaac
118021 gctaaaacag agaaaacacg taaataacat gtctgccagg tagcaagcta ttccaagaca
118081 aggaaggaga cttctgtgtt tcgaaaaatc tgttttgaaa cacaaagaga gactgggact
118141 gtggctcagt tagtgtagtg cttatctcta tccgagaagt cctgggttca attcccagca
118201 ccgtttaaat ggggcatggt aatagaggcc tctaatccca gtccctggag atagtggcag
118261 ggggactcca agttcaaagt tactcctggc tatatagtga agaatgcaag gcagactaga
118321 ctgggctaca tgagactctg ttttaaaaag ggaggaagaa tccttccaat acataacttt
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118561 aactgggttg agtaccccaa atactcaaaa gaaacagaca atgctaacct gggagattag
118621 aaatgattct gcaactagtt ccctgctgca tgtgcagctg gaggccccca caagttggag
118681 gcttggtggg agactgagaa agcatttgct attcgttttc taggtccaag gcatttcttc
118741 caggatccat gggctggact agatggagca agtgcaggct taagaagcac aggtactgtc
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118861 atccagttct ccttccattt gtaccactac tatctaggac tcactgatct tcagtcacag
118921 gaaaaggtca tctatagcca gtggccagag atagcctttt atgcttgctg cacgacacag
118981 tcagggcagt attccaggaa tgcacagaca gcctgctcag cttctctcac ttcccctctc
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119101 ctgtagttgc aggtatacaa ttgtgagttg ctatttaggt tatggaaggg ctgtggcatg
119161 ccaacagata atgtgtggct acatggaggt aggcatggga aggggcaaat acacacacac
119221 acatatgcac acacacaaac ggaacacata catagacacg cacacacaca taaacacaaa
119281 catgcacaaa ggctcacaca cacacataca cactcacaca cataaacaca aacacacacg
119341 tgctcacata tacacacaca tgcatgtaca cacactcatg catacacaaa cacacataaa
119401 cacacacata tataccctac ttctgtacat gtgtagtcct gactcaggac cttgggacct
119461 gctgctcatt cagcatatgc cgctttctgt tctccacaga catcctgcag atgtcccagt
119521 gacctgcctg ccgcctgcct tccctgtctt tgaggtggtg acaactcctg ccaccccaac
119581 attttatgtc acagcttcct cttcagctga cttgaaagct ttattttgtt caaggtctac
```

FIGURE 6WW

```
119641 cgagcaacca agaaagaaga gctagtgttt cacgggtaca gggtggagtg ttctggggat
119701 aggtcagtca tcgtttccct tttagggaga cttggatcgg tgttaatgaa ctactcacag
119761 gaactggcca gaatcagagc ccttgaattt tatgcactgg tccagggagg tcctgagaga
119821 gtggatgcag agtgcactgc ctttttttctg cctttgcttg gaatcccaga ggagccagat
119881 tccaggaagg aagtggggca gggaggcagc agggtataac gaacaaacag aaaaacaaaa
119941 caacaacaac aacaacaaca accaccctca aacctggtct ggctcagcgg gtaagagcac
120001 tgactgcttt tctgaaagcc ccaagttcaa atcccagcaa ccacatggtg gcttacaacc
120061 acccataatg agatccgatg ccctcttctg gtgcttctga agtcagctac agtgtactca
120121 gtataataat aaataagtct ctgggccaga gcaagcagag ttcctaaaat tcaattccca
120181 acaaccacat gaaggttcac aaccatcagt aaatccatcc atccatccat ccatccatcc
120241 atccatccat ccatccatcc atccatccat cttccaaaaa aaaaaaaaag ccaaaaccaa
120301 aggcatggcc acagaaacaa tgtgtgccta ttgctattag taacaaggta ccttcttcca
120361 tttgggctgt gtgcggcttc atggtagttt accctgtgct gcctgtgttc atttccacag
120421 ggaccccagg atggcaggaa gacctgcagc cttctcacct tcagaaccag agccaagaac
120481 acagagcaaa tgtcatgaat ggtcagagtc acacagcctg caggaggcaa agctggaatt
120541 ctaagtggct gagccttgag gtctcaaagt ttgtgaccaa tacactgtgg tggacctgcc
120601 ccggttccag agtcactgga aatattctca tagcaagcag gaagatctca gggacagcag
120661 acgtagttct aaatgggcat gtcttgctag aaggcacagc tgatgtgcct tttccagtaa
120721 gcattacaag aagcccattt ccatggttga aaaatgcaaa ggattattct gagccatccc
120781 gatgataaag aggacaacaa tttgccttta aaaaaaaaat ggaagctggg cacagtagca
120841 ctcttctgta gtctcagaac ttaagatggc tgaggaagag gaggacttgg gaagaggagt
120901 tcaaaggctg gcaggggaaa acacatcaag accttgtttc agatccacaa cgtaagcaaa
120961 ccagaaggtg gtggcaaacc tggcggcgac gcttaggaca tctaaatact caattatttc
121021 tacttcaaac agtgtaattc gtacaaactg gtagagcaca gaagcagaag aacattaaac
121081 acaggattta ataatggata tgtgcacaca catatacact gttgaagagc ttgtcgtctg
121141 aaagtttcta tgaattaaat atttgttcat taactactcg agttcacttg caaggcatgc
121201 caggcgccaa gggagagcac agaagtgcac aaggccttcc acacaaagac caggaaagga
121261 gatgtgcaca tagataatga gtaaggcaca gacttatgtc ataaagatgc gtatcaggaa
121321 gccaagagca ctgccagcca agaccatggc gtggaaaggc atgtgtaaag caggtgctcc
121381 cggcagggtc catgtatgca tgagaatctg ctggagtgat ggtgggggtg ggccccttag
121441 atccatgcat ttcaagggaa aactatcaat tatcatcttt atttatttat tttatgcatg
121501 tgagtacact gtcactcttc agacacacta gaaggggtca tcagattccc actacaaatg
121561 gctgtgagcc accatgtggt tgctgggaat tgaactcagg acctctggaa gagcagtcag
121621 tgcttttaac cactgagcca tctctccagc ctaattatca tctttactga taactaaaat
121681 gccttaaaag tttaacttag taatactctg tttaaaaggt atataactaa acacagccaa
121741 tctgtttaaa acaacacagt ttcctgagtt gactagaaga tgctagtttt tcattctgtt
121801 tctcctggta caagaagatt tcaaactatc tacaatccct catttaaatt taaaaaccaa
121861 ccaaccaacc aaccaaccaa cctccattgt gagaggtgcc atgccactgg tacctgcctc
121921 ctgctcctcc tattacaagg aaggatggct taatggcctt gctgggctgg gcttcctgac
121981 tgcctaacag tgtggaaggc tgcacaggca gtggagggaa aaaaccccca aacctctgtc
```

FIGURE 6XX

```
122041 gtttgttaaa acaaacgagc attttcacat tcactcatac tccctgaccc catagatcct
122101 gtgaattcta aaaaggacca tgcttgatga gaatgttttt taaacattaa cgcctacaag
122161 gtggagagcc agaagaaggg agccaagagt ggatggcgac cctcttcctc tcatgcttag
122221 caatttctgg tttcactcct atgcttctga gcaccccaac aggaaggctt cacagctcct
122281 gaaggtctga gctagaccag ggtacacatg aatatgctga ttatgtggtg ctcatgcaag
122341 gagaccccta aaagatgact tccccaccta agtccgaacc gccatgactc tgagataatt
122401 tacccaaagt tacatttctg tttcccaaag tattaacaag agtgtttggc tcttttaaaa
122461 agaagcttag tctttcaggg ctttttttct ttccctttc ttttttcatt ttcaacaaat
122521 tgcttctatc gtctgagatc tccattacgg aactgtttgt attgagtttt agtgaaggaa
122581 gaaaaaaaaa aaaaaaagaa aacagagcgg ctgggaagat tcaagtgtgc tggagactta
122641 acattaggat cgggcacacc ccaggcttca gggttaagtt aaggagggtg cttgtgtcca
122701 gtgtgagagg tggggatggg gatagaggaa gcttcctcgg aagacttgac cactcccccc
122761 cttttgtgaa gcctggaccc ctgtcacagc gagtaccaga gtacagcact cacccatgag
122821 cctcaattcc atgtgagcct attctttact ccacgttagt ctgcctcttt tgcaagcaca
122881 ctctgcaact tttcatttta aactgtgtgg tgtgctaacg agagtcagca gctctctgag
122941 tgacctaggc aagttctttc ttccatgagc tgcctccagc aacagagaaa gggggcaata
123001 ctgttgcagg gtcacggcag ttgggaacac ttttcctata gttccagaat tactggtctc
123061 ctacccaaac ctcagatcat cattaagaca tgctaatgtg tagcgagaca ggttggaagg
123121 atctttttct atataaaata ctgctgactg gggcgtggaa cccctgtcct attgggtgct
123181 gtggccatgc aaaaagaggg tcttccaaaa atttaggatt aagagggcat ggtgggagag
123241 gaacaacaaa ctttggaagc cttctcaatg tactgtagaa ttaaaagcca accaaggcaa
123301 ggaaggtgcc ttccaaccta gaaatccagc caccctctgc aacgagccca ggcctgctgg
123361 agaccacgtg aggtggtagt gggtatgcct ggaacctaac ataccacttc tagtaccgcc
123421 cagctggcac ccaatcagga gcggcacagc attctctaag cccaggttgg cacctgcaat
123481 catcttaagc atacaatggc attgatttcc acttagggtg tagaaataac actcagaaat
123541 tttacctatc tctgctgttt tgctgccaaa tttcaaatac tctccaagaa acgcaaacac
123601 aacagaacac ggaggatgtg acacacaaat tctgcacaat ctcactgcca atacctcgat
123661 gttatactca gtgtattaaa tggaatcaga atcctgagtc ccactgtcaa acttcctcct
123721 cgtctagtcg gtatgtgtga ctgacagctg atgtcactga atgcttgatg tctgaaatgc
123781 ctaggattcc tttttctccc cccatccaaa tataacagct ccatttcata ctcctagaa
123841 tttcatttgt gactggttag cacactatca gtgagggaac acgggggctg caggaagctc
123901 accgtcctta cagatttctg ggagggagct caagagtaag taagtgtgta agccttcata
123961 gctctaccaa acacatgcat aaaacctgat taaacacaga ggaagaacat aaatattctc
124021 agtcttctaa ggggcagatg aagtctgggt aagaaggact aaagaaaaag catagagtaa
124081 aattcgctcc cgctttttaa taactcttta agataaggag agttgtttaa tgttttcaaa
124141 ataggcagag agagagagag cgagctagag agagaaagta tgtggtatag tttatgtgtg
124201 tatgtgatgt gatttatgtg tgtgtgagtg tgtgtatgtg gtatggttta tatgtgtgtg
124261 tgtgtgtgtg tgtgtagcac tgtgacagag tgtgtgcttg gcatgtgaaa tcccctggtt
124321 tcaatccttc cccttcagaa tgtttccttt ggaacaaacc aatacatctg gtgacgctga
124381 cctttagtgc ccctcctcca ctcaccctgt tttctacagc aaaagtatct acaaaaagga
```

FIGURE 6YY

```
124441 agccgtgcct caggaagtct tcaccaaagc ttgaagagca tggagagaag aagtaaggtt
124501 ccatcagatg ccttgtgttg aggtaagtcc tccctcccaa tcaacccaca atgaatattc
124561 tctgatgtca gcccctctct ctgagcatcc tgtctctgag accttggaag taagacttct
124621 gtgtctggga ccaaaactac tggggctatt ttggcagctg agccctctgc ctcctctgca
124681 gggaaaaaca gtaggaacat ttcaaataac attcatattt gagatatttt ctggctctgc
124741 gtatttttct acttcatagc acgtgtaatt gtcctccctg ataaaagtgg acctagcact
124801 gctattttaa aagttttgtg ttctacactt taaaaggata cacaaagtcc tagcaggaga
124861 acgtcaatta ccaagtacaa aaacaaaaca aaacaaaaat aggaaatcac catttggcca
124921 atgccacagc aatgggtgtt gaatgaggag gggaagaaat aatgaacagt gtgtttagag
124981 agtcccgaga tctgtctcaa agtacttctt aattagagat aaaaataaag atgttaagtg
125041 acgagaggac cttgcagaga cagcattaac caagtgtcac aattacctaa gcatggggca
125101 tcaggtgccc tggcaggctg acgtactgac tcttcacagc aggaaagagc acaggaggct
125161 gtgtgtgggg ctgcaaggaa tgacctccca tgaagtacct ggatcgagct actgaagtgt
125221 gggaaaagtg tcccggaatc ggagaaatca aggaggacag gaatcagagc tgggtgggca
125281 ccgctcctgg atcaggaacc acaaatggca caagagaggt caaagggcac tgggaagaag
125341 gggcagatgg tggcagtaca gtgcaggtgc taccttcatg gttcggacag cttcatcggg
125401 gttttgtaag atgctaatta gaagatgtca gacacctccc acccccacgt gtgcaaaact
125461 gaagcagaaa tatttcatat aaaacaaagt gtttttttt taagttccta aggtaaataa
125521 aagcaactta gtgacatatg gaacacaatg tccccgacag tttgacaata aggcaacact
125581 cttccttcgg gaggagagaa atctctactt tgcgtaggga cacatcaagg atatgcttct
125641 ttggaaggtc ttcaggctgg cagagctggt caccaatggg gatggtgtgg gggcgtttac
125701 gttctcacaa ttccccatct atctcatgtt accctccagt gcaacggaag tggagggtac
125761 actgagtgtt catgaagaga aagccgttaa cgagatgctc aacgagaata taaccatctg
125821 tcgcacttgt cccgcatgtc ccatgccctt ttcctaggct gcaagcacgc aagtggtaca
125881 cagatacaca cccaggcaaa acatccatac aaactaaaca cacacacaca caccctttt
125941 gggtcctttg gagtccttgt ttatgggagc agacattgtt ctgtcttctg tcacagatag
126001 catcctctga gcttggaaag tttaacatga gattgatccc actctttcca agggggagag
126061 ggagactaat gtgtaagcag acagctccca gtatcacaag ccttagtttc ctcatctatc
126121 actatgtggt ggtagtgagg gcagtaaaaa gaccttgtca agctttgact agaacaacct
126181 gagattcttc attctgggag tagccttaaa tgtaactata ttcactggca aagaagaaca
126241 aactaaggcc ccaggtgaat gtaagaaggc taccattttt acttcggtga tgctgagtgt
126301 taaggcgtgt atagcacaac agaggagtac tccaccgcaa agggatgcac tgtctctttg
126361 gagtcgaggt gcccccctcca ggtaatgaga cagaaaggag tggatacagc tggtccaggt
126421 tcttggctgg ctccgagagc tatgctaagt cctctgaatc aatggtatga cacaagtttg
126481 ttctctgttg agctggtgtc ttacttcatc accagtgctc atctctaact cccgagctca
126541 agaaatcctt ctgcaggatt ggagagatgg ctcagcggat aagagcactg actgctctcc
126601 cacaggtcct gagttgaaat ggctcacaaa ccatccctaa tgagatccga tgccctcttc
126661 tggggtgtct gaagacagct acatgtactt acatataata aataaataca tctttgggtt
126721 ggagcgaacg gggctgggga gagagacgaa aaagtgtctg aagatagcta tagtgtactt
126781 atatagaaat aaataaatta aaaaaaaaga aacccttctg cacagccttc tgaatagctg
```

FIGURE 6ZZ

126841 gggtttcagg cttgagcccc ctttagagac aggcagcaga gacacaaagg cctgcccaac
126901 atgtgtagga ttagatagcc tgggtatggc tgaagggaac aggtactcag gttggcccag
126961 gccaggagcc agactctagt atattatgca aggttgcctc ctaaattata atgcacttca
127021 tttgcagaga gtccaacact agactcatgg tgtctggtag cccagagggt aacaggctgt
127081 gttcttcaca gggaacatct gaggacagag acggaccaag agggctcttg acggtggctg
127141 gtggtaagga ctaggagcgc ttacggcgag ctgcttggga gaagcctttt caggtggtta
127201 tctgagagaa ggcacaggaa gtcatgaaat taggacctga ggacttgtcc aggataggcg
127261 cagtagtgag aactgcatcc ttgtgaagat gggtttgacc tctgctggag gctacaatgc
127321 agctaaatgt gtctttatct taatgactcc agaaacgcca tgctgtgaaa gaagcaggta
127381 ggtagaggga ggtcaggaga gcaaaccaac ctcacgtgaa gggtaactca cagacttgtc
127441 gttcactttc cagaacccaa ccctcaaaag aacatacttc tagggtgtag ctgggaacca
127501 ggaagcagcc agctctgagc tgctgcttgc ttgctctctc acacagtggt aacaagcaat
127561 gctcatctct tttcaaagca ctccaagcaa ataaacacct gcagaggagc tgatggagac
127621 agacttctct tactggggtg agtctattaa acagaaaagg aggcataaaa atgataaacc
127681 cagaccgtca gaacacagtg agtgcaagaa actgtcagca gagagcgaac tgcttccttc
127741 tcacgccgga gggcactgct ggattaagca taatacaagt tatgtatgct cgctgatgtt
127801 cctgagcggg taagaaataa ccagtgttca ctagagtaaa aagtgcagcg gttctgaatg
127861 catgctggaa agatctccag caagggacag tgcaggaaaa cgggagcaga agtctcagcc
127921 ctcggtctgt gtatcacctg gtcacgcttt ctcactgagg gatattggtc cccgggcatg
127981 agaggagagg ttcctgctac ctagtgactt tctcaagact gacttaccac taacctgtct
128041 cctatagtgt caggagcttg agtctgaaac agtcttcact aaatttttgg ctgtaactga
128101 aactggacta agtaattaaa aaggtttcaa tatttaagct cacatttaag ttgggaatgg
128161 agggatggtt tgatagtgaa gagcactggc tgctcttcca gaggacccag gctcaattcc
128221 tatcacacat ggaggcttag aagcatcttc ttcaggagaa gacctacagg ggaactaata
128281 tccttttcta gtgcacacat ttaaaactga ggcttagttt aaaccctgtt ttaccagggg
128341 caggggtgtc tgtgcacaag aaagacagac agagtttagt tttagttcta gacttctatt
128401 tgctcaccag gaaaataaca ttggtagact ttaccaaaat ctgcagcaaa aactaaatga
128461 taaatgtact ctcaaaacag ggctcaatat cccacaggtg atcagggtca acttttccag
128521 ggaccctggt gtcagtgggt tttatacttg gaatgagaac acagtaaagc tgggactgcc
128581 aatattcctg ctaggactct ttattttctt tatggcttcc cctagcttat ttagaagaca
128641 ggcttctgtc cctcagggac tggacttctc aagagcagaa cactgctgta ggaaacagtg
128701 tcttccaaga gtcaagggaa ggaggaatgc caccactgag aggagatggc ttgctttcct
128761 ccctcaagaa aagagtgagc aaggctccat ccacggcgtg ttccaacacc ttcccacata
128821 gctggaccca gatgtcatag gggacttgca gaaaggaagt ttcaacatca gctagccttg
128881 gcagatgctc ccaagtcgtt caaaaataaa actcgggcga tgacggtaaa gatgggatga
128941 cggcttaaga tggagcaaga ggctttcccc gtggcgggcc tcagcttagt gctatgcccg
129001 cttgccgtct tgttcaggaa caaaccgggg cccagatgag aaacgcgctc gcgttgacca
129061 tccagaaagg cagagtgtgt gcttctgaag gcagtgttct ccagcctttc taccttccat
129121 taaatggttg agtctgtcct tgtgtggatt gatgttattt ctaaagcaca caattcattt
129181 caagagggga gaggcaggat taagctggaa atagtttttt ttctattgag aaaaaattaa

FIGURE 6AAA

```
129241 gtgtaagtgg aaacgttttc atgaaaatgt ttttatatct caacgtttcc tgcgagcact
129301 ctgatcccaa tatatcacag gactgagctg gatgagggag aatgaaggca aaatgaattt
129361 aaataaaatt gaaactgacc ggctaggctt tattctccaa atctcatgaa atagcaaagc
129421 tgaggggggac agagccacaa ataaaccaaa agaaaaaaaa aaccaaacaa acaaaaaaaa
129481 aaaaaaacaa gaagcaactc aacgctttca gctcaaatga gtttcaattt tatttcaaaa
129541 tgttttaaaa tctagtttat tttcatagcc acaaaagctt ttgaatacct atgaatcaaa
129601 agccatttgg cagaaccatg gagcttgtcc tagttgcttt ctctcaaact cttccctggg
129661 cctgttaacc ccttgttagt cagtcacgca cagcaggtca ctctcagtac ccagttctta
129721 ggggcactct acagccttag tgtgtatgag caggcagagg ctctaggctg gacggcacat
129781 ttttaaaata cacattttta agtgtatgta tttttttta ttagtcttaa ataggatagg
129841 gaaaatgata tatacagact ttaactacta attactttag acaaagaaca aacagaaaac
129901 aaaaaacaaa aacaaccccc tccccaaacc caaaccaaaa aaaccactaa aaaacaaaac
129961 aaaaaaaccc caatccacat cctttagaga ttattttgtt aatctgcatc ttgatctgtg
130021 ctgctcaggg gccacaggag gccacaggag gcctctgaaa cttgaaacag ttaagattaa
130081 gtaaaaagtg caacgaagag agctcaccac atcctaaatg tttctcaact actcaactcc
130141 cggctaccac acgcagggca gacacagggg atctgtcgag gcacaagact acagagtaac
130201 agtgcaggtc agacagaaga gcaggggtgt ggtctcagtc cagctctcac atagctcatg
130261 ctggcctcaa tttcgccatg tctctgaaga tggccttgaa ctgatcttcc ggctcccttt
130321 gggactgcca ggtgtgtgtt actctacaca ggttacgtaa ttgtcaggcc tttgtgtttg
130381 tgtgcatttc cctaagcaac ttcatgtaca aagctaagtt gggtatgcat tctctcccca
130441 ggcctggccc cttactctct accgtaaaat gcttcttccc taacaacccg acttgagtgg
130501 ggtccctacg tacagagaaa ggagatattt acagaagaaa gggcaaatga ctgcttttac
130561 agggaaagag catcccaggt caacacacgt accagattgt agagagggca ggtgtctcca
130621 tccccgtgcc tctctatttc ctttccaaca ctcagccctg tgtgagcaga gagtaaggcc
130681 cctctttgat gctgcacccc cctattataa gcacaatgct tgtaaccaaa cagatggttg
130741 gatgtttggg aaatgactga atgaaacaaa agaagaatgg tattctgtta aacaacagcc
130801 aacatccctc tagagcctgg acacacgtct ttatagagcc tggatacaag tctttatatt
130861 ggatagcaac ctctttactt tcaaatgcaa tctcagagca acccagaaga ctgattcagg
130921 tagtatacca cagctcagtc tcttccatgc tcaacaatgg ctccttccaa atggcattag
130981 cgttgtctac atatctgtac agtcagagct aatgtctatc tgttcgtctt taaatggccc
131041 agagcttttc actttccata tactatttca cctacccttc acctggatat tgtctataca
131101 ataaagagga ggaaaccaag gcttgggcga aactgacttg ccagatcaca tagagttata
131161 ggtatataaa tggaaaagct ctggtaaaga ttacagacta tgctgattct attagctggc
131221 tgtaggacag ctgaatggat ctctttcaag gaagggcatg atttgtaagc atcccacacg
131281 tcagtgctga gtaaggctcc taagtcctgc tggcttgctg ccagccagta gacccccttcc
131341 agggtgaggg aactgggcag agctcagcac aacccagctc acctaactgt ggctgtcaga
131401 atcattggat cctgcccatc atacatccac tctgtggcca tatcccgcag cttcacaagc
131461 ttcatcaggg tcgggcctgt gtctgcaaaa agaccagctt gagaagacca ggaggtgtat
131521 atcaagtacc actcgttcat tcgttcgttc attcactagt cagaacttca aaccaataac
131581 cccagaagta aagacaaaaa ctccctctgc cctctggtgg cttgaacttc cctcttggac
```

FIGURE 6BBB

```
131641 ccaattccca caggttaggg tttccagaag ctttcaaaaa aaaatcactg atgaaacact
131701 agctctttag cttagcgtat tatacaaaag gctgatttcc gatttatcaa agggttacca
131761 aataggaagt ataaaaaccg tatgatcctt acagggaatg gtcaaagagc agtgatcaag
131821 tccctgattt acataattct cagccattct tttggcagac ctctacagcc actaacattt
131881 ccatctacgg atgataaaaa gataactctt ccccttcct gggtgcctgt caggtataaa
131941 cttgaagccg ggcacagtta atcctcacaa ctccccaagg aagaggtatt accatgtttg
132001 ctccagatta agaaagaagg gtcaggcctg aattccaggc atcagaattc tactgagagg
132061 gaagagagac agacagacag ctttcactct ggcctagagt gcagagaaaa ctactacttt
132121 ctgtgggaag aaaagtcagt caaccacagg aatcacagaa ggatccatca caagaggacg
132181 ccactgtccc ttaagcagag acaggactga gaagaacaaa ggtactactg ggacagaata
132241 tggagaggtc agcttgagga agtgctctag caaatggcat caaggaggcc atttccccaa
132301 ctggagagag acctcagatc ctcaccacag gagccaggta gcactgtggt acgcacacat
132361 accatgtgtg tactgatgtg gtgggagaca caggcagagg tggcagggtg aaatcaggtc
132421 aagaagaact gagagccagg ccggggccac tgctctgccc tgcttatgaa agccagggga
132481 ttaagtcaag acttcactcg tgattcaaaa agttatctga agacatggcg ggaagtacag
132541 ctaggtctca ccacccctcc ccctcccccc cagctctgca tgctcaactg aggacgtgcc
132601 acttggcacg ctggcactct cctacaggaa aacatacttt ggctattcag acgtgacttc
132661 ctggcactcg gaagctgttg gcatggaaaa attaacaggc tgacttggcc agggaggaac
132721 ggttaacaca aatcaccagg aaaagatgag ccctgagcaa gcgggaggtt tgagggaagg
132781 gtcacggaaa aaagaagggg taagacacat ttgtcaggag tcccaggctg gtaccaagcc
132841 cactgcatga caaaggtcat tgagccctca cagccataca cagacatcac ggctttcctt
132901 tcaggcagtg gacaaggagg ctaacggagg tgaacttact tggcctggat gaggcagcta
132961 ataagggaca ggagctggta cacacatcat cacaacattc ttcattacgg tctctttctg
133021 ccttcaaccc cttgcccagt ttgtaacttc ataaggtggg gtaatgatgc caggaacttt
133081 gtagccctga ggcagaactc tgccccagct gtggccttcg taacctcccc ttactacaag
133141 cgacacagcc acctccactc aaatcctgac gacagctcag tatataacgg tagcgtgtta
133201 catactaact tggtcatttt ggggaaagct gcttgtgtgt gtaaaggggg gggggtggtt
133261 tggggcttgg gatcaaacaa atgagtaagt aggaaaaaag accaaccatc cactgagatc
133321 ctaaccaggc tttcataact taagactgga gtcttccaca aactcacaca ggtagccata
133381 gaagctactc ctggaaatcc aatcctggcc agaacatgct agggccaccc acattcctac
133441 ctgcagcaac cttcctttct ccctcagcat caaccctaag atcctccagg gctctgtagc
133501 tcagtaactt tgcagggtgt taagtctaga ggagcccaga ggtccgtggc ctcccatgtg
133561 ggggttacaa ttcctacaac cttaaatcct gtaaagcgtg cccacaaggt ccttcagctt
133621 ctcgccagaa cttccaaacc ttgcctttac acttaacaaa gcttcctact aaatatctac
133681 accaaatttc cgtacattag tttttctttc tgcttgtgaa aggggtggtg gtggtggtga
133741 aactagtcaa gatcggatat cctctgcaat accagcttct agaaaagagc gtttttgaat
133801 gggatgccac gtgctgtgtt ttgccatatt gcctgcgctt cctgcttgga gccagagtaa
133861 cagaaacctt gggcactggg aactgttccg tgccacgcaa attccactcc gtatcttcca
133921 ggcaaccctg tcgcaaataa ttcatgtcca ctacgccccc accacacaga atacaactac
133981 attgtgctgc tagaaatggg aaacctgatt cagatcagag aaggtagaaa aacatttagt
```

FIGURE 6CCC

```
134041 tcaacacaat actgccttta tgaaaagggg cgtgcgccgg gtggtggtgt aaatcccaaa
134101 cctgtaagtg gggatagatt tcaagacgaa ttttggaaga aaatgcagaa tcaaaatagc
134161 atccagcttg actcagacca gtaataataa taacaacaac aaaaacccag ccagtccttc
134221 tagagctacg cctgtttagg ctgcgcggtg ctcttaatgg ccagccagcc tgttctcctg
134281 ggaaatggtg ctgctgctac agcgtgactt gctttgcgtg ctgcaataaa aggaaaacaa
134341 gcttgcacga cccaatagct tccttcagtt tgtgcctagc agcggggaga aaattaaaaa
134401 aaaaaaaaaa aaaagcctga aaaggggtcc tgaggcaagg tgaatggagg acaggatcct
134461 agagaacagc actgccctgc aggatttttg taaacagcag cctgtaatgg ccacggttag
134521 agaaagaaaa acagacatgg agggaagcgt gtttacaact gcagcaaggg cgggaggcgg
134581 agggagggat tccccggctc tgcgctcggc cctcttcact ccggtggggc cccggggttg
134641 ggctgagctt cagctcccca ccccaatccg tgctttcttg gggggccccc catcttgttt
134701 atgggaaggt tactcctcct cggctctggt gatcgcgtcc ctaatactcc agctgcatcc
134761 ttgcgggatg ccagcttgac tgacaagtcc tgcagccaat cgctggttgg gcccttagga
134821 aaggtggaat ttcccaacaa actgattggc tgagagagag ggcgggccct ggtgattggc
134881 gtgttattcc gagtagaaag tagtaaacaa ccttggtcca ggggcggtgg ggagggcgcc
134941 cggtgccagc tccctctggc tggcagggcg gggtggggaa gcacccgaga caaaaggaat
135001 cctggctgcc acagcgggga gggcaggaag ggggtggccc caaaagtcag cacctggagg
135061 cgtcgtttgg agcccccccc ccccccccc cgagccagaa ctgctgactt taagccacac
135121 atcgtttttt tgttttgtgc agaacctcaa aggttttgtt tccatcattt tcacttcttg
135181 tatggctgac gaagtctcca atggaatgat aaccgattta gtcgcttttg tccagaagcc
135241 ccttcctcac cgtcgaataa aaatttaaaa ttgtctttta cgaaagttgc tttaaatcac
135301 acactaaaat tgttgcacta tacaatacgc cattaatggc atgctggtgc accagacaca
135361 cagctacatc ttttgatagc aagttttagg agctctgagc ctattgggag cagctgggat
135421 ggagaacata cacaaaaaga aacaacacat gacggcgttg ggaccacttg ataagaaata
135481 agcggttaac ttgccttgcc catagtattt ctggcagtct cacttgaatc tcccattccc
135541 tcactccagc ttcaccatcc ttacaggacc ccaggcggag gaaaccatct gctcttagga
135601 tgggggggctc tgctcacccc gcacataaac atgctcacaa gtcgctatcc tgagcaagcc
135661 tcctcaatgt aaaaggggac caggaggcca gccaagccgg ctctctccac ttcaatgctt
135721 gttgaatata cagagaccac gttgtcactt ttcacaatca agatatatcg gtatcacgat
135781 atatcgataa cgggtacttt ataggagata acagtgcaaa ctggccacct ggcattctcc
135841 tttgccattc tagtccctca cctctgctat ctcctatgga gcctgccaca agcaacccca
135901 gtaaatgttc accccaagtc acctttgctg tataaaacat ggatttaggc tttccttggt
135961 ccttgcagcc tggcatcaga ccccaaacca gtagctactt tcattgtagg caccctccct
136021 ctggacactt tgttctgttc ccaggtccct gcccagacca cacacatcat tttactcaac
136081 gttggttttt atgctttcta gactttacct ctgcctgccc aggagaggcc actgttctcc
136141 accgttctcc ctggcccagc taccccactt cttgcagaag actgaaattt gttttcttag
136201 cactaagtct ctgatagggc tttaatgctg tatttagact ccactcctac gttaagaccc
136261 tgaacttcct gaggcctgga atggtattat cttcagattt gggtcttcag tggagatggg
136321 cttctactaa agtgcccgct gcaaacttgc caaatatttc taggattctt ccctagcatc
136381 ctgagtatgc ctacccctga aaatctttcc ttacacacgt gcaattaatg tgttttctct
```

FIGURE 6DDD

```
136441 gctgggtcaa caactctgtt ttctctactt ggcaaatttc cactctgcct aaaatcactt
136501 cctctcttgg catacctttc acaacctccc accaactaca ctgtgtacca agagcagaga
136561 ggtctctttc cgttcttact tctctggcca gaattagcta caaaactaga actagcatgg
136621 tttgttggta aaggaagagc ggagaggcaa aatttcagaa gtggtatcac ctgtacatct
136681 gcataaccaa cccattgcca tctgtagggg tgaagcagcg ccatgctccg tttgtggctg
136741 tgatggtctc cccctgcttt ctgtctgaag gcctctgtct ctgaggtgga ttcttactcc
136801 cccctccatc tcaatcagag atctcctcct ggctcttatg ctatcaactc tgcacatccc
136861 cgattccttt ccaccatgac actgaactgt catctccttt tctatctgac cagtcactga
136921 cttgctcaca gtttagtctg tccgccatac agccatatcc agtgttctaa gaattgtggg
136981 gttccacagc tggggctcag tctctgctta cgccctcatg tgacatctgt catcaaccct
137041 ccatctttct aagcctttaa tggtggaaaa gagtaaacct gtagataaag agtggtacca
137101 gatttcacct taagattaca gatacttgtt tgtgaataga atttgttctg gtacaggcaa
137161 atgcacggtt taaaatcaaa actaacaaaa tatacagtat attagctggg aacaaatagc
137221 caactaaagc aatgtaaagc tgggagtctg tattctggct caaagcccat cacggtgagg
137281 caaacatgat ggcctgagct tcaggatgct cattaccaca ctgcatcctc agtcaagaag
137341 cagagagaac tggttcccag gacaggggct ggtgctgcct aagtcttggt cttcccgtct
137401 ttaagttaac acggcccttg gcaggcatgc ctgaagcttg acttttcggt gattacagac
137461 cctatcaaac accataaata ataacaccac acatatatta catatataaa aactataaca
137521 cagaacactc aattggcttt cagtaagtgg gctatttttt tttctttgtt gcttaatgta
137581 ttctagatct gtctatgttt acaaacggta tgtcttctct actaacaaat aggatttcaa
137641 attaaaaagc tgaacagcaa aggagacagt gaagagacaa tctgttagct tttcatctga
137701 caagggatta atatactgaa tatataaaga acaaaattta aatgtcaaaa gaacaaataa
137761 tcaaaccaat aaatgggcaa attaatcaaa tgggcagttt tcaaaagaag cacaaaagac
137821 caatacatac atgagaaatg ctcaacaccc ttagccacca gggaaatgca aatgtaaacc
137881 acaccgagat tcaaatctca ccccattcac aatggagcac attaagacaa ccatcaacaa
137941 acactggcaa ggatgcaggg ggaaatgtgc ctgtacacat tgttggtgga aataaaaatg
138001 aagtagttta gatactatgg aagcctatat ggccaaaaat gtgctactac ctcacttcgg
138061 gatgtacaga tgtgatgcta agtcagcaca cgacacatcc acgttactat ccacatcagc
138121 caagcaatgg gaccaggaaa agatgaagga aatgtgatgc acacgcacag ctgtgtcaga
138181 tgtcaaggat aaaaccaaac tatcggcggg aagttaagga gtggacaatc atctgaagtg
138241 acgctggcca gaccaaagcc tatctcatct gtgtattttt ttttttaat gaaaataaaa
138301 gggaggcttt gtacagaggg aggaaatgat acagaaggga aagaagggac aaacagaaga
138361 taatgggtgg taatcaaagc acattttgta tatggatgaa agtattaaaa caagaaaaca
138421 gccatcttat cttcacagac agcattctgc tctatagata accctgagtg gtccccaacc
138481 ttgcctgtgt gtttaaatca ctgttacttc cccagaagcg gatttagttg gtttagaggc
138541 tatcacgtga gccttgaaat gaaacagtag aaacaaagtc ccagatgatt ctaatgagga
138601 ggcaggtttg agagataaca gtaaacctat ttattatccc tctactgata gaacttgtca
138661 tttcagacaa caccatgtaa agtggcctaa tacacctgtc agttcaccgg tgtgctggtg
138721 tgtctgtggg tgatcatcct gggagaatta ccatgtcaaa gggcacaggc actggtacat
138781 cagaaatgct ggcaaattac attccattac acacacacac acacacacac acacacacac
```

FIGURE 6EEE

```
138841 acacacacac acacacacac acacaccatc ttccagcccc ctctgccaag tggggctgtt
138901 ttcctataga tctgtcatca gaatctgtga ctgaacattt tagattttca agcatggggg
138961 gctgggagga gctctgaata ctcataaaaa ggactttctg atgtgttcta ctacaacatt
139021 tctggttctt ttgtttgttt gttgttgttt acacctttat tatgaattca cttagagtct
139081 aacaaggatg gacccatgat ccaacatcag ttaagtaaag agcgtatttg ctccaatgat
139141 ataaaacgtc atcttattaa acaacgaacg gccacatgtt ctcacatcta cggctggata
139201 tcatattctg tcccttcaca tactggcacc ttgctagcta tttaatcatt aattacttag
139261 gcaccatggg atgctttaat tatctggtaa tttcgttggg cttgtttagc actattacta
139321 ttatcaccat tattattgtt gctattattg acgactgtag agtcagtttg tataattaaa
139381 agaaaccaca tagtatttga agtatattaa ctttataaac acaggaagaa ctgacatctt
139441 gctaacattg gttagactcg cattaaaggt atggttctat catttatttg aatttatatt
139501 tggcagcatt ttgttcagta ctatttttct tattaatttt taagcatttt tctctgggaa
139561 aaacttttct tctatgatgt tgtatagcaa attatttgca cactgtagcg ttatcacatg
139621 actaagtctg gcttatgtta tttccagaag atgcttaatt ccatgccctt agaatctgag
139681 catgtatgca catgtgtgaa cccacagggc aactctgggt gctgttcctc cctccaccct
139741 atttcagaca ggttctcttg ctgggctgta gcacaccaat gaagcaaaca agtggctggc
139801 cacaagcccc aggggtctgt ctacctctgt ttctacataa cggagatttc aagcttgtgc
139861 cactgtgccc gtgattttta agatagattc ttcgacttga agtcagttcc ccacatttgt
139921 gtggcaatca tgccattgat ggagctattt gccaagttcc ctgtgctctt agaactctca
139981 ataaataaac gacaccaaag gtcttttccc ctcactagta tgaagtttat tatttttttt
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140761 caattcaaac caataaattt tgacttgaca tttacaacgt aagcaattca gatgtagggc
140821 atagcactag ctggtagagg caagactgga tatggggagc ttctaaccca agagtggaaa
140881 gtgttgggag aacaagactg agggcttggg gcagtgtggg tgaggtggaa agctaactgc
140941 gtgccttagt gcatgcctta ggaaagtatc tcagctaggc tactatagca gctatgcatc
141001 tatctatacc agagaaaccc cacagagctg gacatacaga tgagctcatt catgtctgat
141061 gagctcattc atacacgtga tagccatgat gttctgctga acgttttatg agataaaacc
141121 aagtttcctg tttcagagct gtgtgtttaa aggtatgtcc ctttatgaac attaaacaac
141181 cagctgtatg tggtggtgtc aataatccca gaacaagagg gctcatggaa gaagggtctt
```

FIGURE 6FFF

```
141241 aacttcagac tagcttggaa taaatagtgc aaccatgtct caacagacaa acgtaactaa
141301 aatatcatct tacaaaccaa gaggtcccag cataaatatc agagcagagc tgcccagcct
141361 tggtctcatt ccagacctct taacctatga cctcttgggc tgaggtcata gtcggcatag
141421 ggaagtgcct ggctagtaac aacaacacag tcacacatat ctgtcctcaa ggagctcctc
141481 gagtaaacac ctttgctctg atgatgacaa gcatggccac agtccctgtg cttgcagaat
141541 cttggttaga aagctcccaa caccaccatc ttccactagt tagcctctgc tgttccccga
141601 actgaatccc taagtaccga atgctctcct gttccacaca gaaacctctg agaagcccag
141661 tttacagaat cagagactgg gccattcctc gaagcattgc taaagaactg gcaggagtca
141721 ctcaagttct caggagctat gggaagataa gattctcccc aatgcggttg cactgaaaga
141781 cagggcagta aagaacaatt atgcctaacc ccgatttctc tctgaatcca tttattactt
141841 ctcaatttag gagagtcact cttgtacctg caccctggcc actactcaga aaaacattag
141901 tgtatccaat gatcccttta gtaactactg gagaagcagc tagctgaagc atgggggaat
141961 taaggaagac cttaggagtt caaaaccccа aagtacaaac gcactgtcag cacacggaga
142021 gatctgtttt tttatgcatg ccttatgcaa actggcctaa gctaaaaaat gttataaagc
142081 attttgagga gtaaattttg atttcagggt taaaaagaaa tgtacagagt caaagaatct
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142861 atatgtgtct aaatacactt ttttcccctt gttttgagac atggtctctc tacgtagccc
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143221 cacgtggatc cttcggcttt gcttctgtgt ctcagctacc tcagaggttt gctgtggaat
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143341 aaaaggagat tggcatgtag aagcttcatt aaacttttgg ccttttcaaa gctaaacgag
143401 tcttaagaaa agccataaaa agttcccgtt gattgattta aaaacaggct ttttttttt
143461 ttttttttt ttgcaattag cagatctaaa tctacgaaag ggagaaacac gtacggcact
143521 tttagttaac ttcctgcttt ctctgtgtat ttcaaatcgt aacaattaag actctctata
143581 gacacacgta cagatacaca aatacttagc aggacgtaaa cttctatttt ggcttcatga
```

FIGURE 6GGG

143641 aaatggtagt tatgtttcca cacacacaat gaattctggc agtttattta caagcagaca
143701 tcccatctgc accagggata ataccctcaa ctatgtgaca tgctacatcc ctcctgaaca
143761 cagtagggct aggaaagcac tgagaggata taaacatgtt cagggcttac aatattcctt
143821 cctaatgctt ctttccccaa cttactgtaa cgatttactg gaaagattgg actaaattac
143881 cgtcttccct ttatcgtccc aatttgtttg catttggtat cctctccttt ctcttggaat
143941 ctcccttgct tttccttttg tcagtaagtt aaattgcttc tcctcccaca tgcataaaag
144001 cattaattta taaaacacat agctgtatgt catatctcat gtaattctat tttacatttt
144061 accactagct agacttatct aacatgaaca aatagatatt atttactgta gccagaatga
144121 gaattatcta atgccactta catagccaga aattgatttt tgattaatgt ttaagcgaaa
144181 agcaaacaaa cccatctgct ctgaaaacaa acaaacaaag aggagcagag cactgagtcc
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144301 ccccagggga aagcggacca ctgacaagaa caggactcca ggcccagact ggagtttctt
144361 ctccagcaag tgttgagtaa aagatttttt acttattggg gggggggggg agacgggacg
144421 ggactgggga ccacaaacaa caacaaatct ctaaaccctc tcaggatcag cagagaattt
144481 catcttgggc gcccactgga agtcaaggaa gttgttaatg gtcatgtttt ccttcttccc
144541 tcttgttcac taggtcagtt aaaagacaaa gaaaaaggct gggcatggtg gtgcatgcct
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145201 ccggcctcct ttggagcact ttcaacagcc aaaactgaca caatacatac gcatcaacaa
145261 gcaagctgaa cacccaccac cggtgtgctg agagaagaga ctcaaactca caactttcaa
145321 agtcccatac caagcctgat gatgcaaaca caacttgaag tcttattggc gacgctccgg
145381 atactaccag ttgctaaagg aacagagtgg gactgcgact gcattctgaa acattttcta
145441 caaatactca tcctgcacga agaagtaagg tgcaagtgcc tttatgactc tatttccact
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145861 actgaccaaa aaaggaaagg ccaaacaagt cttaaataat gattgttggc gtaccaactg
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FIGURE 6HHH

```
146041 ttataaacac tccctcagtc cccccaaagc aacaggaggc aggcacaatg accctactga
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146161 aaaccagctt taatatggat gccctttcct tatcaaagac agcagggtaa tacggggagg
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146521 aaggtagaag cccctgttca gaacttttca aggagcagat gaagacaaaa aaatgccacg
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147181 gtgaaactgt tgtttgccac tgcctctctt aggtagggtc taactgtact cctgactaat
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147661 tttccagttt ctcccctcaa agatcttcac atcatgagtt atgatactcg ttcattacat
147721 cctcctagaa tggctccagt caagaagaga aggctcaatg acccacccca actgcaaaag
147781 caaaattatc ttagaagaag aagaaaagga atggaccatg taattaaaat tacgaggggc
147841 agtgacttac agaggtaaaa agttaatcac aaggactatc tcaaagccta gtgaaaaatg
147901 gggttttcag aatcagacct gtcaaaggta accacgagat gcaataatgt ggtttggaag
147961 tctgggtgac gggcagcagc aggaacaggt cagggaaggg gggagtaaat tgtttgcaaa
148021 atgaaatgca gaatgaaaga ccatttgagc acacaggcat ctactctaaa acctgcaaat
148081 acctcagcct cagtcctctc acggaggact ggggagtgtg cactcttctt gttgctttag
148141 aggaggtctc tgctgcagaa gcagggtggg tgggtagagg ttcctactga aagctacttt
148201 gggtatccag caccccgggg ttggtagcaa ggagtcccct taatgaataa atgaagctgg
148261 agctttccag atgtttcatt aatggggcac ccagaaccaa tgctgctgca cccgtgcccc
148321 ctacaactac taccggcatc tgggagcact tagctctaaa gtaggttaga gctggagtgt
148381 aactgtatct atgtgaagac tgagtttgta tatgggaagc tcagcataca gcaaggccct
```

FIGURE 6III

148441 acgtgctggc tatcactgca atccaggcaa aggcttcctg gaaggctaac gaactataac
148501 ttggctgata atgccgttcg ttcatggctt cgtgagcgct ccagtcccgg tggccttggc
148561 gagagttgga gttgagtgga gactgcaggg acggaaactt ttccagcaag aaagagtccc
148621 tcttctccca cggtcactaa ggaggatact tgtatttttc caggatcagc tgagtcgtca
148681 caagaggaga gtggaggggc aggaggagac cgcctcaggc ggcgacaagg gagcccagca
148741 cctcccctga agttgcagcc agctgcttct tggctggaaa cttatttaag ttgtcctctg
148801 tcccacttct gaggctctac agggatgctc tgggcactgg gatccatgaa caaacaggga
148861 tgagcggagc gaagggaaca ctctgctcag atgagtctgc ctctcaacgc cctttgccct
148921 cactgtgctg gtggggagtg ggggtggggg aatctgatgg gcaaaagcaa ggggcggaga
148981 tgtgactgtc acgcagaagg tgtgcccagc tcttagaaaa gtgaagaatt caagaaagca
149041 aacacaagca tctctcctgc ttctactccc tagttatccc aatcccaatg aatcttggaa
149101 taattttagt tactgacact ccagatagca tcttcaacag tgaagccaga agcagagcaa
149161 agggatctta gtagcatgtg ttaattttca tgcaggatgc aaaacaggca tttcaacttt
149221 catctttctg gatgcagcta cagtggccac catccctgac caggactctg tcttcatctc
149281 atccttctaa cagttatgca tcaagagtgt atcagtaacc atatcaccat gcaggatgtg
149341 taacttgcct cttctctccc gtttcaggac agccagccac tggaaagtct gaggggcccg
149401 gctaactgaa atctgcagat acgcttagga atcccctccca accagccggg ttaacctcca
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149581 tcacttacag aaagctgcag gcaaagtaaa tccaagtctg ggcagcatat aataaatggc
149641 tagtggcaga taatgaaaag gctgaaatca caaaatcaaa attctttcca ataaaggtga
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149881 ccaggccagg tgatgaagac atacccaggg tcattctttc accatgacaa agacatctcc
149941 attgtttcaa agtcactttc agtctcctac aaagttatct ggagaatagt gtgccatgtg
150001 aatgaatgtt caaacttaag caagggtacc accttccttt cagaaacaac cagagaaata
150061 cgaaactgcc tctggggcat cgcaataagt agctggggct ggtaagctcc aagtcttacc
150121 tctgaagtca tcagtaagca tgggacagtg aaggctcaga cataacatct catccaagta
150181 atcaagagta acgccaccca tcacagatgt actggtgcca ccctgggcac agtgacacac
150241 cgagggcact gtataccctt cctgaaggag ttaatcactc aaatgcacaa acctaatgtc
150301 acgagagacc ccagtttaag agcaggttat ggggtcatag gatgagtgct cgttaaaagt
150361 gacaacacca tgcaaaatca gcaagacaag cagacccatc acagcctcga gaagaccaca
150421 cagataagac acatccacac gaccaaagac ttgggaatga aagaaagcac gttagtggga
150481 aaactggtgg aatttaaata aagcctgcta agaatattgt gccaatgtta gtgtcttggt
150541 tgtgataact ggattatgat tatgtaagat gttaacatga ggagagctgg gtgacatttc
150601 aggaactctc tgtgccgttt tcaacttttt ctaaggtttt ttttttttt tttaaatgaa
150661 gctgaggagg aagcagagag cctgggaggc tggcttactc tttagtttgc tttgtcactt
150721 tgtccctggt aagtagggtc attatactac agagctggct tgtgttacag ctcttccgat
150781 tttgctccct ccatgtcttc ataacttttg gggaatcgga tgttactcag gtgagacaga

FIGURE 6JJJ

150841 agatgagtga agtcacaatg tcattggaga ttagagagag aaagagagag agacagacag
150901 atagacagag agagacagag aacaaacttc aaatttataa acacattatt cttccacaaa
150961 ggtccacatc acacactccc cccatttgtg caccaccctt gacaacacag ctgtgtggtt
151021 ctctagaaga tgtagttgga accaactttt agcgtcctaa ggaatgatgt catcctttgc
151081 tctataggag ctggttccag aggttttgtg gaacagcttt ctttccagaa agcagccagg
151141 tctgaagctg ctcagacttg ctctagactt cttctgtcta cagagtacgg caacatctcg
151201 tctacaggga ctgcgactgt tccggctctt tgatcatcct gttccctaaa cttaacttcc
151261 ttaagttgca aaacatttac tcttggttgt ttgggtcctt cctcggtata gaaattcata
151321 ttctctgttt ctctctctct ctcaacgggg ctgtggactg aacttacgtg aacttcttgt
151381 gtttgcctgg ctttcactga ccctacacct tcagtccttt tcctttgtac ggagaaagaa
151441 atcattaaag agaaaattgt tccttaaaat catccctttc cccatcctcc aagccttctg
151501 tagaaagtgc agtaatgaaa aaaagatgtg tactcacact ttgcttgtat cagctatgga
151561 tgggttccta cctatcttat tgccaaactg aaaaactact tggaaaatgt tccaatgggc
151621 tcggtagaat aatagctcca agtcagaact ggggtgcatg gggtgtgtat agtctccaga
151681 gtggggaagg ctggctactt gtcgggtcct gccctatcag cctaccagtt actacgctgc
151741 tcttccctgg cagctcagtc agtgtgcggc gtggtctctc ctcctggcca tctaaaatgt
151801 ctgcagttat tgtaacacag gatgtgattt ttagatcaat ataaacctgg tgaacagatc
151861 aatcctgtcc ctcataaaca caggcaagta tctgggtatc tagacggtca tgacctctaa
151921 cctctgaacc aaattctcaa cccaaaccat cattagcaga ttgagcccaa gtaaatgcat
151981 gtgtgcagaa gtagaggttg actccttctt aactgctagg tttataccag ctaccttatg
152041 gggtgcccca aataccatct ccaactaaaa ccctttcagt ttaaagggca aagggccctt
152101 aggtaaatgg ttcatttggt gaggcctcct ctctttgagc agtcacatga atccacaatg
152161 gagaaagaga ctctaactcc tgggatttct ggtaacctaa agagttccat gtctttccta
152221 cacaattggt ccccagacgg ctcaagtctt attgaaccga tatatcaatt ctggtggagt
152281 taaaatgctg agtaagagaa aataaagctg aagtaagcgt aaagacaaga gttgttttgt
152341 tttagctgga acatgattct ttgatgagaa aactctcata aacaggaaaa agcacattat
152401 tgaagctgaa gtgtttgatg gcttccattt tcctaagagc atttcgcctt agacacaggt
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152521 aggtcctact gtgtgccagg gattgtagtg atagtgggga tacaaagata ggagttgagg
152581 ctatatacac tcttttcaaa ggcaaagtct cgagctctaa acgcacgact caaacacaaa
152641 accatgatat gcaaaggaaa caaatggttt gtttcttggg gacaggttga acagtaagta
152701 tggtgacagg ttttaattag aagacttcag aagagcaggg ctgggccatg taaatcaaat
152761 cctatatcag ggtctgtact aaactcagaa agactaactc aggcagttac tagagttatc
152821 atgatcctac acagaagttc atataaggac cctaactctg aaagcagaga tttgttgttt
152881 tgtttttttt ggctgcctct agctagcaca tttatgaaaa acaggttaag ttactggctc
152941 caaattactc cttaataaaa aaaacaaaca aacaaaacag cataagcttt taagatttc
153001 ttttttaaaa cctagaaaac agtctccctg tcaagagcag gcatgattaa tgacttctgt
153061 gctgtaagct tgggtatccg ccgtgttact agtgtgtgat actcctaaca gcttgtaatt
153121 gccccgagga tacttttgga actgaaaggt gtggggcggg gcctaccttc ttaatatctc
153181 cataattttt tgggggggggg ttagactaca tttatcaatg ggacattgaa aatacagaaa

FIGURE 6KKK

153241 cattgtcaag tcatccacat gaaattatga atgcattatc atctgaagag tcatttccat
153301 aaaacggcag atgacaaata gtcagctctc agtatccatg ggggatgggt tcaagatccc
153361 tccctcagac atgaaaatct gagatgagca agtttcttat tatagatggt aaatctgcat
153421 atgatttaag tttttcttcc tgcatactag aaatcagagc tagatggttt gccatacttg
153481 agagcgcaca aacgctgcgt aaacagtcaa ccgtacggca ctgcttagag cagtggttct
153541 caaccttcct aacgctgctt ctcaaatgct gggaatggaa ggtgtgtggc accatgctca
153601 gctagaatcc cattgtaagt atggcactgg ctggacctac atctgcagaa ctccagggta
153661 ctgaagggct gtactgcatc ctagcagctt cctaggtctt aggaagctac caacctgcaa
153721 actccttctg aggtgaaacc acaacagggc atccaccaaa ctcaaccact ggaacccaat
153781 gaaccagtca agttaacaga acactgagcc acctttttgtg ctccatgaca gccctgacag
153841 acaacatagg caagctctat cacactgtat ggctcaacca gccatatttt ccatagaggg
153901 gaaatggagt ttgctgcttt gtttggcaga tgcaaagagt aaagtagagg ggaaccaaat
153961 gagcttagag cacttgggaa ggtaggctga cttcctagtg tgttccactg taccacgcaa
154021 tcccactatt agctccccac ttcctctggt caacaccaga tctgaacgaa acctacagga
154081 aggtttgaag gtacctggcc ttctaaattg tggcttacat aataacatca ggccctctgg
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154201 cttgtgtttc aagggaaaat aggaaggtgt ggaaagcctc cattgacacc ccaactaact
154261 tgcctttgct tttctagaga caactatgca cttaagaaag gcaatcgaga tctgcagtta
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154501 gtcattcact gaattatgta actgactcct agaacacact gcagacccca tatggaataa
154561 gacagcacaa ctcctgcatg catgatcact gctgggctgc aggaatgtgt taagacacat
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154681 cctgggcaca cagaacttgt gcatcaagtt aaagactaaa gggccagagt ggggttgaca
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154801 ctattttcag cagagagaag agagaatgtt attgagatga aaatgtggat ggcagattcc
154861 agtgcaaggg gtgcagatct catagaaggt gggtcaggga tgtggggttt gaaaatggct
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155101 agaattaact ccatgggaaa cttagtggaa ctgaggacaa cgtgtcaact acaaagacca
155161 gaaagcaggg ctagttagat ggctgagtga ggaagggtgc ttgctctgac ttcaatcttc
155221 aggagtcaca ttccaggctc tatctccaca cgtgtgctat ggcacgtcca cacatagagc
155281 aaccaaataa ataaacataa cattgaaaga taccagaatg catgctgtct ttgaaaaccc
155341 tattcattgt cttaagtata agatgacagg gccatttccc aaaaccatac atcttgtgga
155401 gacacaggtg gggcaaaacc aggtcaagtt cagtggacag caggtaccaa atggacttat
155461 ggctatacct ggtaaggcaa gccatgaaga tgatgagttc tggctccctc gttcttcggg
155521 aacctgaaat ctggagaagg gggaggggggg aggaggagga ggaggagaag gggaagaggt
155581 agtggtggtc actggtggac agggaagaac atctaggagg aaagaagcta cagaagttac

FIGURE 6LLL

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155641 tgacggcagg agagggtcct tccaggccat ggaaacactg ggcctcaaag gacaggctgc
155701 tccagtctga tgctgcatca gaaacccaca gtcaatatat tgaaggtgga aatctgaaaa
155761 gcacttattt ttataattaa atacttttat gatagagaaa aaagcaaaca gagaaaaaaa
155821 agcaaaagca tcaggtttca cccaaacaca gcaatggtca gtttgggttc atctgagatg
155881 accaacaaat gccaatatta gagttacagt ttttcaaggc cataattgct acatttaaaa
155941 catcaagagt cacagactgt ccccaaacag tcagagccct catgacctgc ctgtcccagg
156001 atctgagagc tacagtgttc tgcttctatt tagagcatta tgaatgctaa atagaaatgt
156061 tcaaaatatt ttacaaaatg aaaagtagac atcagtccac tgcaggtcta aggctgttct
156121 ccaactttaa aatacattag ttctttttt tcctttcccc tttttctttt ctggagacaa
156181 ggtctcaggt agcccaggct ggcctagtat tttatgtgtg actgagaatg accttgagct
156241 cccgattctc ctgcctccat ggaccaacga gtgcagttct ttccccttaa gagtcacata
156301 gttgaaccag gaaggatggc tcatgcctgc aatcccagca ctcaaagggg aaaggcagga
156361 gggctgtctt gagttcgaag ccagcaggga ctataaagtg agctccaaga taggctgcgt
156421 tgcagaatca caacacgtct caaacaaaca acgtagcaga catatctaac ccttaagcat
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157261 tctaacacac acacacacaa aacacattag ggtaaatatg tattagaaaa acctttgcct
157321 aagatttcct ttaaacagtg ggtattattc atttttgttt ttttctttac agaacattaa
157381 tttctttgca aaatgtttgg ggtacagaga ttgcctgaca agagtggcca ccatgaagct
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157681 tgcatctcct agtacatttc tggctacagg tgaactaaat gacaccaaag aactgctctc
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157801 cttaaaacgc agtcaaagtt aactgtcatg tccatagcaa ggaggaactc actccttagg
157861 atacactggg ctggtcttcc agtgggcatt tcagagagcc ctgctttccc atatcagctc
157921 catcctgtat cctcaccgtt gcttccaaca gggaaccgtc cacatctgac tgcccaatca
157981 gatttcagca ggtggcatgg gggatccaga aagcatttct ctgcaccttt taactctgaa
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FIGURE 6MMM

158041 ctgcatgcag aacccgtggt aagaaatgct tctctgatcg ctcctagcac ttttagtggc
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158161 taattcacac tatctccaaa taccctgaat taccaagtct gagggctgcc tagattcctg
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158281 ctggttcact gagaaccaaa catcatctaa acagaacaaa aacatcagaa ctgaaggaat
158341 cgccaaagta tatacacgtg actcccgtct gaatgcattc agatccgacc agtgactcca
158401 agctttctgc atgtttccca tgagctattt gccctgaatc aactcctcac cacaactctc
158461 gaaatgacat ggacctctgc tgttgcactt attattcctt ctctgatggg gagtggttat
158521 gactgaaaat tttcgcgcaa ccagcctcta aacagaaatg cagtttattc tgagtactca
158581 aattcaaatc tcagtaacac agcaattaca ttttaaaata aattctctcc atgttcttgc
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158701 gccaattata aaccccatat atgttcacac atcaagcagg gcaaactgct ctgggaacaa
158761 cccttaatat tttattgcct gcccaggtgc ctgagcactt ctgagataca cctgtcacag
158821 gaaaatacag cacttccttc catctttacc ccatagttgc cagacaattg ggcagagcta
158881 aagtgggtaa tgttgcagtc aacacttccc taaaacattt atacatgcca ctgataaaca
158941 atagaaattt aaaggagata caaatgtact ccccaaaccc taaatcttcc tcccacggag
159001 gcctaaaaac ttaaaaatct tcatctacct ggcacagaag aaggaataca aattccaagg
159061 ggagcctaga tttatggcct aaatatgtct tcctctagaa tatttaatac acttacgctt
159121 tagtcattcc atacattttg aaaatactct agcacgataa attacagtag ctgcatcttt
159181 catggttgtt cacataaata tcatttggct ttcaggaaac caattacgga gcggtaaatc
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159421 atatttcaca caggtattag gctcagcaag tatttcctaa cctcctgtag tatttagttt
159481 tcaagacttg gggtaggatt gggaccacat tgatttcagg gtgctgactg tacttctgtc
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159601 atggtgttct tgagaaatca agaccatcat ctcattggaa aggcggtggg aaacaaggtg
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159721 tggactggca tactatatca atttggaatc ccctcggcta tgacaagttt gtgaaatgaa
159781 agaacaaaac aatacagtac aagatcaagt tttagtagag agaatgcaga caaccacaac
159841 cgagtactta gggagaaaaa aaaaaaaccc agctcttagc tggggagtga cagtcaaggg
159901 gggaaatcac gcgaaggaat ttctttcagg tgcaagaagg catgagagtg ggagacaagg
159961 attgagcatc ttggcagaag gatcagaaac ccagtccaag gtctacactt ccgtggagca
160021 gccgcagaca agcttaggta tccggtgggg ataacctaca gttaagacat cacattacag
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160141 acacaacaac caagccgtga tctagagcag gaagcggggg atagacagaa agacaggttg
160201 taatggagga gaccaagcag agggctgcat taaggcagag gcttctgtgc tgaccaagtg
160261 actaacacaa agggcccttg cagaagacca gagatgtcag gggggagaat tccttctgag
160321 ggggcctagt tacactagcc acttgatatt caccgggaag gaggcagaga agctaggagg
160381 gtgggcacaa aggcagtggc tctcttctac ctgaggagag ctggcagctc tatcaatacg

FIGURE 6NNN

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160441 gactactcct aaatgggctg cagtcagccc agaaaaaaaa aaaatcactc aatactctca
160501 ggttacctac cctggctccc aaagctggtt atgcaagaaa tattttgttg ttgttttgct
160561 tttaaaagga gacaactgat gcttgtttta gtattgtttg aactacatca ctcacaaatg
160621 agagactgat aaagagattg acaagtctga ctctagaagc aaacacttcc agtctgctct
160681 catctgccct cccccacttc ctccattctc ctcggcctct accccacaat atgcttgaaa
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160801 ccagagagaa aaaaacattt tctggaaaga ttttaactac tggatcataa acaagcgtgt
160861 ggtggccacg cagcaatctt tgtaataacg aatccaagac gtcctggttg tgaagcccag
160921 tgaatgtaat gttagctgaa aagcaccgcc tgacacacct ggaaatgtgc cacgggccag
160981 ctttgtagac tgcgacttca aagggaaact ggagtctact tccgcttttc agtgagttag
161041 aaatgatttt ggctgtattg gtagggcaga accagaaaat aagttttgaa tttgtcataa
161101 taatttacaa aaaccaacca acttgttaag atgcatcctc caagcacaac taagctggct
161161 atagaggcta ttctgcattc tgcatctggt cccctggact gctcaggctt agggtgaggg
161221 aagaaacatg acttaagcca ttacccttat tctgtgggca tttgaagtgg ctgccaggca
161281 cgtgacacca actgttccaa ttggttcaca atgacatcac tttattattc aactctgttt
161341 gcatttcagt ctcctccttt ttcgggggac ttgaggccaa tcctggccaa gtcactttag
161401 aagagaaaga agccagtctt aggtagtcat gaagtgccaa gtgtcttttg tgtctcctag
161461 cctagtttgt aagccgggaa ctggtgacat aaagggctct gtcaacagcg cccgggtgtg
161521 ctgcttccct cgcagcggga gagggagatt gggaacccag tagaaggtgg cggttcggcc
161581 ttgggtaggt cccaactgac caagttcaat aaaatccctg agagtttgtt ttcaattggg
161641 taagaaaact ataaaatgga aaccgcatgc gagcttacgc tggaacctca tttaaagcac
161701 ttgtacttcc aaaaaaaaaa aaaaaaatgc agaaaacatt tctaatttag tcaagcgcac
161761 tcttctttcc tcgagcaatt agtcttaatt catgtcacct aactactatt tctgcattaa
161821 gcaacgtgac ctctagaacc tacagtaacc ccctttctga tggtgaaagt caattattct
161881 gatttttttc atcttcacac aataagttac cagagaataa actaacttca aaaaagcatt
161941 acagtgtcat gtgtgttcgc ctgttgatat gtgcacacat tcatggcacc tgtgggtctg
162001 tatccagctc ttctactgtg cctgtctctc aattttgcag ctcaacctag agatcaccaa
162061 gtggccagcg agctccatgg atcagcccgt ttctgccctc ctctgtacta agattacacg
162121 caatcatgct gagcctctaa gaacatggcc gctcatggtc tgaactcgga tcctccacct
162181 agcatggcaa acatgttagg aacggggcca tttcctcaac acaaaggaaa aaggcttcct
162241 catgggagag aatgactgga tgggcgagta gacagatgaa aatggacttt tcacaccaac
162301 tggttagaga ccctgttgct tccaggcaca aagcacacca gtttctagta tcagtgggtt
162361 gaaatgcatg tttaagctct ctcatcctta cttggctctt gacaggaaac ttttatggtt
162421 gaactttatt ctgtagaaat gcagtggcat taaccaagca cacaaagcca actcaagcct
162481 aaagtgtgcc catgactcca accctacact cattggttct tgccagaggc aacacgaaac
162541 agtgtataga ctcagaactc tgcccaggcc tgtgaggcag ggccagggct acacaccttg
162601 caaacacaca gcaggctctg cccaaggagc gttcactagg taactatcag ggtggctcaa
162661 gggctgtacg acagacagac cctgcacagg cagggaaagt ttcctggaga cctaccatct
162721 attttcttgt aatctcaact gatgtgttct gccaagtcaa ctattattta tcatttataa
162781 agcagctcct attggcagca tactctgcat atgtttcagc acttcataaa ccctccacgg
```

FIGURE 6000

```
162841 tataatcgct tgtggaggag actgggttgc ctggagctgg aatacagacc cacacgcatg
162901 tgagcccgtg taaatgcaca catgaccgtt ccctaccgct ctttcacgag tcatgtcttg
162961 gctctgtagg ccgagtatct ataactaaag ctctctacag gtgtcaaatc aagcaatctt
163021 ggtcctctca gatgtcagct aatggcttag agccccccc ccctaacagt tctatttgca
163081 ttgctaacca aggctatcca ccttagtatc atcatcagtg caagagaagc caaactgcac
163141 acgaagacct ggagagcact tcagagcaca catccgacct cttcctcatc cgagtaccta
163201 gcaagccagt tttccttcct ctcctgtctc cagaagaagt tccaactcca cctcggagca
163261 aagcagcagc tgcagtgact agcagtgact atgcctttgt gactgcgtat cactcatcca
163321 attcacagac tacttagcat cgacttgtat acactttgcc caagaataaa tatttatatt
163381 cccgaaacac agtcgatcga gagcagctga tacagggctg gagatgacag aggcagcaaa
163441 cacaaacaag taagacctcc aggagtgtga gggacagggc tagagacaaa gtaaacagag
163501 gccacaagat cctaggcgct aggtgggggc tactggtacg taagggctgc tggaaagaag
163561 agtcctccgg ggactggctc ccacaaaggc tgcccaatct caagtggtca gctctgggcg
163621 cttgtctaga tggcaatgct gcgtggactc agtgggttat gtatgcgtgt gtacatgcac
163681 atgctaggat aataattaaa aataagaggt catgagtttg ggaggttgga gtttgctcat
163741 gggagcaact ggaagtgggg ggcagagaaa gggctgggag tgacacaggt gtagttcttg
163801 tgtatggtct aaagattaaa ttagagttag ggaaaaaaaa accccacagg aattgggaag
163861 agtgattccc aagccactga cacagcacag cactgcttgc ctgtggaggt gctcctgtgc
163921 catcctccct aatctttatg ttgcacatct taagagtggt ctgtttgtgt atcctctcat
163981 gcatgtatct cctcagcgtt ctcatccacg aatgcttaca ggtgacgtta gcatcagcag
164041 ttggagaaca agatacactg gaaagaaaac attgtaccct gatttgcacc gggaagagga
164101 gaaagggaac acgctaagca tataaacatg ttaacggtca agtagagtcc aaatcagatc
164161 ttgccactct tcaaactgaa ggtctgtgat acttaaaagg gggaaaaaac ccattgaaat
164221 gcagaaggca gagaccatca ctcaaagata ctcatcgctt ggaggtcagt ttatatttgg
164281 aacagtgact tgggattggc caaccatcac tcatgccatt aaagtaatat ttcagtttca
164341 actgttttac atgcatttag catgtagacg tattcaattt atagttgtaa acggtctaca
164401 agtgtaagaa gccgataccc aagcttcgaa tttgtaggtg tttaagtcta agtcccaatt
164461 cataccggca ctacaggtca gcaagtgtat ggtttttaac tttaagaggg cgctcaataa
164521 actcggatag aaaatctggg agcaccaggc cttgttgtga agctactttc aaggcgatga
164581 tcctcatcgc caggaggaag ttggtttata cccatcatag ttcctttaac acaagcaatg
164641 cagaatggcc ttcacaagtg tctcctctaa aatgactgtt taaattgtgt tgtttcaaaa
164701 agaggacatc cacgagccgc atgtttccat tatcccttgg aactggagct acaggcagtc
164761 aagggcttcc ttacttgggt gctgggacac aactctggcc ctcatggtag aacagcaagc
164821 ccagcaacct ttctagttcc aggattaggt cttaactttc gtggtctctt gatggcacac
164881 agaaattgtc tagaagtcag aggctatgta cgggtggatg atgtacaccc agtcgccctc
164941 caagcaagcc aaatatgaaa gcaatttttt ttttcaaaaa taaaatagca ccacactgct
165001 ctcccaccag gcgtgtagag attttcccca acaaaatatg acacacatca tatctatgat
165061 tgcttctaaa tgaagaagtc tttaaaagtt ttaacttctt aagggccaaa tatcaatgga
165121 tatattccat ataaataaaa attcatcaga tttgtcttca cctattttgg ttgctgtaac
165181 caaatccatc aaccaaccaa ctaaccaacc aatcaaccaa ccaaccaacc aaccaaccaa
```

FIGURE 6PPP

```
165241 ccaaccaacc aaccaggtag tctctgtctt gttccagtcc cattttcctg gtgcacaaaa
165301 ggactgattt tacttgttag aaggttatcg ggcaattctc tgtgtctctc ttacaagggt
165361 actaagcatt ctcaggaggg ttcaatcttt atggcccaat cactcccctt cgccccaaaa
165421 caatgtcttg atgaccttcc aacacagtca tggcagatta tggtctgtag gctttactgg
165481 tgccaagggc tcctgagaat acaacaccaa agtgatctca tcccaagaag gatgcttcag
165541 acagacagtc ccacatgctt tcctctactc ctggctcatc ccctgtattc catacatcta
165601 tatcccccgt ccctcttagc tctcctctga gtggcaaaga ggcatctccg acttaacgag
165661 atgcaaggca gagttctagc tccatctgcc atccccacca cacacctccc aaacaaacct
165721 actcccttcc tcctgccagc tcgggaacgg gcaacttcac ttctcgtttc atctaagcca
165781 aatgcctgaa tcatccttta tccctctttg ccccacctgc aagatttcac aagtccctaa
165841 atattcctga atctatctac tcttagttac tgtaactgat gggtgcagtt ctcaacaagg
165901 aactcttctg tcccggcact acctgcatcc agccatgtct agatacattt ttcaattgtg
165961 tctgcgtaga caaggggtag atgtaccacc agtatctagc aggaagatgc atagacaagg
166021 ggtagatgta ccaccagtat ctagcaggaa gaggccaggg atattgatag acattctata
166081 atgcacacag cagctcctat catcaaagac tgtccagctc aaaatgtcaa tggcattgag
166141 aaactgagct ctattccaag ccagtagaat ctctccaaaa aaaccttctc aaaacaactt
166201 cctaactgtt ttccctgatt tttcactctt aattgctctg ctcgatgaaa acaactaaag
166261 ttatcagcag aaatacagag tgtgacccac tagagtgctt tgtcttgtgt catggcctgt
166321 aggcccttgc ctactccact ggcccccggc cagctcctac attctcatcc caccaaattc
166381 ctacgtcaga gccctaagcc ctcaggtgac tctgctagag acagactcta cggtagtaac
166441 tgaaggttaa gtgagcccgt aaggaggaac tgagccttgt aatggttggt gccttcatga
166501 aagacacacg gaagcttgct ctctcatcca ctctgctgtg aagcttgctc tcccatccac
166561 tctgctgtga gaagatggcc atccacacag aaaaaggacc tcactggaat ttgaccttgc
166621 tggaactctg atcttggcct catagttcta ggactttgag aaaagaaacg tcagcagctt
166681 aagccaccca ggctgtggta ctttgttgtg aaagcttgga ctaatacatt caaccttgct
166741 accttgccaa gttccagttc actggccatc agtccactta caccacagcc cttgccctcc
166801 ctcttctgaa ctgccattag ctgacccctа ataacccctа gtcaaaatgc caccctcccc
166861 aggagggact gtgttactcc atccttcctg gattttgagg acagccccat ggttggcatt
166921 aaccaagctg cctaccctct ttgcttactg gtctccttga cccagtgcag aaacctctca
166981 gtcttgcccc ttgtcgaatc aggataagat aatctgtgtg gcttatatct cttaaactca
167041 aaacaaggaa aggtaggggg tctgtgaaca tgctttgccc catgacccag ttccctctgc
167101 cgcttctcca aagagagcta ccatacttat gcctaccttа gtttcccaag agcccatcca
167161 gggcaggagg gaatcattac atgtaacatc tagaatgagt acttccttat attctttcac
167221 tttagggagc agcaaaggtt caaggttacg gtaaagtaca ggtatggggg catcaccctg
167281 atatgatgaa gcaccaagga actccccaat gttaactatc tagccacaga gcaggtaagg
167341 gtatgctcca gttagtttta cgaggtcaac tctgaacaga ggaaacaaaa gcaagcagta
167401 aaggactatg aggcacgtgg gtttgtgctg tgtacagccg agcagtcaca gatgcctcac
167461 taaggaggtg gcatggggac taagagtgac tggagttagc catgggaaat tcaggcaaaa
167521 agcaaggaag gtctctctga actggtgagg aacagcagtc gtcagtcagt attactgtcc
167581 gttatttctc tacactggcc ccaggcaggt gcttttgaat gactggctgt ttgcaaaggg
```

FIGURE 6QQQ

```
167641 aagtccagat acagatggcc gaatgagggg ccacgagcct gtgcaggaca tacagataat
167701 ggaacaggaa ccttgcaatg ctgagaccta ctacgtgacg ggtgcttaac agcttttgag
167761 gttaacggtg ggaatttctg agagaatccc aaagagagct agctggttgc ttgaggccaa
167821 caagggcaag gcttataagt caggggcacc ccagaaagga ggcacacccc agaaaggagg
167881 cagcttctaa gaaagaggaa aagagagaaa gcaggcaagc ctgagaaatc aggcttgggt
167941 ggcctgaaaa ggcagaccat gatgtgtgtg gtgggaaagc agggcaggac tcctcctcct
168001 tctggaggaa tacatgtgct ggcactggga catccagctt caaccccagg agcccaggcc
168061 cagcatgacc tcctaacgca ctgtttagta gacagggtag agcctttaag aatggtggct
168121 cgatggaggc cctgtcccat cctccaagat gtctaaaggg ggtgggactg gctaagtccc
168181 tccttctctt cctcaccccc tccacatcca acctcctcca aaaacatcaa atattttctt
168241 ccataaataa ttgcaacagg atgccattgc tttcctcaaa gaaacaatgg cctgattgtg
168301 ccctgtccga cacgggccca gccccagcac acacaaaggg tggctttcag aagccctgct
168361 gtagagaatg ggggtacacc tcctttcttc tcttctgtac caagtccact gccctccacc
168421 aggaaaggac atcaggaagg ggctgctacc acaggaataa ttcccatcag aggacagcta
168481 tcattcacct gcctttagat tgccctttgg ccacctctag aaagttcttc gttctggtga
168541 acagaagagc acctattggc tctaaaatcc aacacacaca cacatacagt tttaggctgg
168601 agatatctat aatttttttt tctaattttc aaacttattt gaaattgtca ttaattaact
168661 tttaaaatat ttgaaatcct agcattcagg aggcagaggc tggacaattg ccccacattt
168721 gaggccagtc tggtatacac tgcaagttta ggtcagccag gcctatgtag tgagctcctg
168781 tctcaaaaaa aaaatacata agtaaataaa aattataaat agataataaa atagtcccat
168841 tttacgtgta catcttcagt ttcacaattt gagataaagt gaatacagat attttcattc
168901 agtatctgtg gtagtgccaa cactggatgc tcacacaggc tcatgcatgt gaacatctgg
168961 tccccgtggc tggcacagtt tgggaaggtt atggaacctt taggaggtgg agtcttgctg
169021 gaagaagtga gctaagccac tgggtgcaga ctcggaggct gatagctggg ccccacttcc
169081 tgtccgctct cctgtttctt caccccactc cacttcctaa gtacaggaag cgcttcatct
169141 agcttcctgc ccctgccacc acagcatccc agattaattc catggaaact ctaagtcaaa
169201 ataagccctt tattacttaa gttgtttttg taacactaat caagtgtgtt tcttggttaa
169261 aaaggacagg ctggactaaa ggattcaatt tcagcactta aggggctgga gagatgagag
169321 agcctgctgc tggggctgtg ggctgggata agttgaggcc cgagtttagt tctcagcacc
169381 catgtttggt tcccaacatt ccatgttcac cccaggcctc caagggcctc cacacacata
169441 gatataccca ccctgagata ttcgcatgca tataaataaa cataaaataa atatttaaag
169501 aacccatcac tttgcagcca tggcttgaca aacaggctct ttggtgtctt cctcacatag
169561 gtgcaagagg aactcaggca ggggtgttga gtttttggat tttgcactta tttatttatt
169621 tattggtggt actctctgtt tattgggggа gttgtggtgg gttgccattt gtaacatttc
169681 cattaaagat gttaaaaggc tgccttccca ttttcaaaga ctcagactga tcactctccc
169741 agccagaggc ttctgtcagc tactaaaggg ttcctttccc ttctatttta tggcctttct
169801 cccatccact tctgctttgt tcttttaatt aaaatgaaat gtaggccctc catggctgag
169861 atgctaataa ggcccctgaa agtcatctgt gagcacatcc actcttgttt aaagagccat
169921 gtaaacagac cacagacggc tacagagagc aacgctgcac agggcaagga aaagggaatc
169981 tggctgcacc gtacagtgct acgttgaagt gatttatcac ttatgccagg aggaggaact
```

FIGURE 6RRR

```
170041 gaaacacaaa cgcaatttca agtttaagca tggcgtctcc acaggatctt ccatagcaag
170101 cactctgcac tcgggggctc cctgtcagga aactcctgga caacggttgg tttgccgtct
170161 gatccacttc agttacctca ccaaacattc aagaggtact ttctgatgtg tgtgggcttt
170221 agcgctaggt tgatacaaaa cagtacctgg atctgtactg gaagtcaact atatttgctg
170281 ccaaatccat tgtaactggc tctgcatgga gccatccgtg tgagagaggc tgatgtgtct
170341 gccaccactc tgcagacact ggaaacagcg caggaccaat ctgtatccat cgttcctacc
170401 tgtttctcag tgggtaacat tctcaaagca ttttcagatg aagaatttag tcagacagac
170461 agacagatgg agacacggat cactggaaga ctgctgtatg gggccacatg gggaaacact
170521 gggttagtca ggaagacacg gcggtttcta cagggaaagt ctgggtgtcc ctttggagtt
170581 cttgtgtgag aaagttgtcc ccaaggtatc agtgctggga gatacaagtt ttttgggttt
170641 ttttgtttgt ttgtttgctt gtttgtttgt ttgtttcaag acagggtttc tctgtgtagc
170701 tctggctgtc ctggaactca ctttgtagac caggctggcc tcgaactcag aaatccgcct
170761 gtctctgcct cctgagtgct gggattaaag gcgtgcgcca ccacgcccag gtgggagata
170821 caagttttaa gaggtgggcc tggtgatagg ttcttaggcc actgggtacc ctgtcctcag
170881 agattaaggt aattctcaca agagggctag agaaacgggc caagtgtgac ctctctccac
170941 atctgcttct tatgtttact tgctctcagg ttcctgtcac tgactcgagc aagagcaacc
171001 cttaccatag ctgcactatg atgtttggac ttcaaaacca aactctggac attaactaag
171061 atttctcttt ttaaaatcag taatacactg ttgactaaca atgaatgaat gaagcagagt
171121 aagtaggctg aggatggact ggttcaagtt atcttggcag gcagtgaagt tgggtagtgt
171181 acggcttccc tggcatgtgg ccctagggag accaggacag aagaatattg acgcagagtg
171241 tgagaggcca atcaaggaag tgtgggggct gagatatgtg cttctttact acctaggaat
171301 ctacgagaat ctcttcaggc tcagtcgagg ccccccaaac ggcaagcctg tctaagtaca
171361 ggaaacaggc aagattaata tggaatagtg gcgcaaacca attagctcaa aaatttccac
171421 aaccccatgt attagccctc tgctcagctc agggagataa tgagaacaca taacggaagc
171481 tcccagttca ccaatgcaac tggggagcgg gggggatgg gtacctcaac cactcttaat
171541 gagtctgtag actaagataa cagaatggca gtcttccatc aacatgaggt aaagctagca
171601 tggcacctca gcctttcaaa gttactgttc actgaaatgt tattagaaaa attgccaatt
171661 gtgataaagc ctatggatca aacactactc ccattgcaag gaacattcat aaacagaaag
171721 ctgttgtcag tccccgaaac ttaaactgta tagagcagag aaaacctgga agagggaagc
171781 gccataatac ggatgagaaa acagggctag gggctcgtaa atggcagatc aggaaggaat
171841 cccatccgcc ttggagttgg tgatcttgta atgttcagag aatggactca tttcaactca
171901 caggttcggt gtgacccacg tgcttgctga agcaccgtgc ttactgtatg gtgctacaca
171961 agtgaggtct ctcataagct gcagagacac agaaaagtct caagggacag gtgggtgcat
172021 gtgtccaaga cctggtcgag cagttaatac gtccaggttg tggcttgtgc tctgcttcat
172081 tagtgtgttg ccagcgacta ggaatgtgac ggctaccacc ttgctgtttg gactcatttc
172141 atggggtaac tgcagcaggc acagggaatg agctaagaca gaccctgggt gagggaggca
172201 gctcatcttc aatgcccgga gagcacaacc tatctgatct gatatactct ccagtttaca
172261 aactactgac aatcacatca agtgaagggc agctgcagcc acagctctcc cttgttcaca
172321 gtttgctttc cttggttcta gttacctgaa ggcaactatg acataacaat attaaatgga
172381 aaattacaga aataaagtag ttccttggcc tcaagttgcc tgccactgga agttacagga
```

FIGURE 6SSS

```
172441 agccatcttg ttgtcctgct ctgtaagggt cctccctttc tgcaacggat ccaggctgta
172501 tacccaacca tcggctagcg acgtcataga gatctgagta gaacaagtgc tgttgttcaa
172561 gtacccctga ctttacttaa cagtgacccc caaacgggaa aaagagtagt gttggcaact
172621 tattacagcc aaaaacatgt tattacaatg tatttttatg actgctgtat tgatactgtt
172681 aattgctggt tataattaag cttcgttata gatacgtatt tataggaatt agcagcatac
172741 atcaggtttg gtggtattta tggtttcagg aatctactac agatctttga aagtatctcc
172801 ctcacaggga gagagactac tgtaccattg ctcttcaatg gtgactccta atactggcat
172861 atagacagct ctgctgacct tttagaagtg ccagagaaca ggcactctgg acacagcgct
172921 gctcttggcc tcgagggatc tgcaagaagg aatggaggga aggatatgtc tctggggacc
172981 agcttctcct ttgaacatgc aggaactaat gagacgcttt ttgaaggagt ccaggtgagt
173041 gacacctatt aaaggtgctt agttaatgct catccccata aacgcccatt acggcgacag
173101 gttcccacta ctcagccgga acgtttgagc tctagatgct cctctgaaga aatggctgaa
173161 aaatcaggga gagatgctaa acccaaacac agtagcagtg ctggcaggag atgagccagg
173221 ctggtgagct gttcgtaaac cagctgtccc cgcccccaag actggagagt acagagaatt
173281 ccatgcaccc agggtcgtct taagacatga acatgctttc agagctgcat ccctaagaaa
173341 ctcctacaaa cctgctccag accatgaccc tgcaggctct gtctcacccc tgcccttcca
173401 ctcagctgct cctgagttac agcctggcta aaatagcaat gctacatttt ctgccatttg
173461 ggggccactg aggcaaatga tcatgttgaa ggggtaactg gctattcact caaacctctg
173521 cattcctcag tgagaggaca gtctcagagg atcccaccag gatgtgctgg ctctgcatgg
173581 tgggtgtcag aactacattc gatttgcagg taccatatgg tgtttgcggg gctggaaccc
173641 tgcttgtggg tattgaaaat cacgtactgg gagtcaggag cgttgtgagt acaaacattt
173701 cagagtgttg agagtgcttg gtgggggttt aggaacaagg caggctctga cttaccagaa
173761 ctgcagcttt tattctgaag tttcttttaa gaaccaagat taggggctgg agagatggct
173821 cagaggttaa gagcacccga ctgctcttcc gaaggtcctg agttcaaatc ccagcaacca
173881 catggtggct cacaaccatc tgtaatgaga tctgactccc tcttctgggg tgtctgaaga
173941 cagctacggc gtacttacat agaataaata aataaataaa tctttaaaaa aagaaaaaaa
174001 ggaaccaaga ttaggcattt gattcattaa acaggacagg ggatcaaata cctccgttgg
174061 gctctcgaga acatgacagg gtggggtgtg cagataagaa ggctctagct agggtagctg
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174181 tcagcccact attctgaact atgtccctgc ccagacacag aggcacatgc tgggcctgca
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FIGURE 6TTT

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1261 ggagcagctg gaggggaatt actccttcta cgtccttgac aaccagaact tgcagcagct
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1381 tcccaaattg tgtgtctccg agatttaccg catggaggaa gtgacaggga ctaaagggcg
1441 ccagagcaaa ggggacataa acaccaggaa caatggagag agagcctcc|t gtgaaagtga
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SNP1507
1561 ataccggccc cctgactaca gggacctcat cagcttcact gtctactaca aggaagcg|cc
Primer 6 exon 8
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Primer 7 SNP1762 SNP1772

FIGURE 7A

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exon 11 Primer 12 SNP2269
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2641 acaagtcgag| gatcagcggg aatgtgtgtc cagacaggag tacaggaagt atggaggggc
exon 13
2701 caagctgaac aggctcaacc cggggaacta cacggcccgg attcaggcca cctctctctc

FIGURE 7B

2761 cgggaatggg tcatggacgg aacctgtgtt cttctacgtc caggccaaa|a cgacatatga
exon 14
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2881 ggttataatg ttgtacgtct tccacagaaa gaga|aataac agcaggctgg ggaatggagt
exon 15
2941 gctgtatgct tccgtgaacc cggagtactt cagcgcagct gat|gtgtacg tgcccgacga
exon 16
3001 gtgggaggtc gcccgggaga agatcaccat gagccgggag ctgggacagg gctccttcgg
Primer 14
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SNP3085 SNP3088
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SNP3154 Primer 15
3181 ctccgtgatg aaggagttca actgtcacca cgtg|GTGAGGGAAGGGCCCCAAG
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Primer 18 SNP3385 Primer 20 Primer 19
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4081 gggccgcaag aacgagcggg ccctgcctct gccccagtcc tcgacctgct gatcctggat
Primer 23
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FIGURE 7C

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Benkel, Bernhard F.

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Cys Gly Pro Gly Ile Asp Ile Arg Asn Asp Tyr Gln Gln Leu Lys Arg
35 40 45

Leu Glu Asn Cys Thr Val Ile Glu Gly Phe Leu His Ile Leu Leu Ile
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Ser Lys Ala Glu Asp Tyr Arg Ser Tyr Arg Phe Pro Lys Leu Thr Val
65 70 75 80

Ile Thr Glu Tyr Leu Leu Leu Phe Arg Val Ala Gly Leu Glu Ser Leu
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Gly Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Trp Lys Leu Phe
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Leu Asp Ala Val Ser Asn Asn Tyr Ile Val Gly Asn Lys Pro Pro Lys
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Lys Gly Val Cys Val Pro Ala Cys Pro Pro Gly Thr Tyr Arg Phe Glu
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Phe Ala Phe Asn Pro Lys Leu Cys Val Ser Glu Ile Tyr Arg Met Glu
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Glu Val Thr Gly Thr Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn Thr
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Arg Asn Asn Gly Glu Arg Ala Ser Cys Glu Ser Asp Val Leu Arg Phe
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Thr Ser Thr Thr Thr Trp Lys Asn Arg Ile Ile Ile Thr Trp His Arg
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Tyr Arg Pro Pro Asp Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr Tyr
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Cys Gly Ser Asn Ser Trp Asn Met Val Asp Val Asp Leu Pro Pro Asn
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Lys Glu Gly Glu Pro Gly Ile Leu Leu His Gly Leu Lys Pro Trp Thr
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Gln Tyr Ala Val Tyr Val Lys Ala Val Thr Leu Thr Met Val Glu Asn
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Asp His Ile Arg Gly Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr Asn
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Ala Ser Val Pro Ser Ile Pro Leu Asp Val Leu Ser Ala Ser Asn Ser
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Ser Ser Gln Leu Ile Val Lys Trp Asn Pro Pro Thr Leu Pro Asn Gly
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Lys Tyr Ala Asp Gly Thr Ile Asp Val Glu Glu Val Thr Glu Asn Pro
        675                 680                 685

Lys Thr Glu Val Cys Gly Gly Asp Lys Gly Pro Cys Cys Ala Cys Pro
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Lys Thr Glu Ala Glu Lys Gln Ala Glu Lys Glu Glu Ala Glu Tyr Arg
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Lys Val Phe Glu Asn Phe Leu His Asn Ser Ile Phe Val Pro Arg Pro
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Asn Lys Glu Arg Thr Val Ile Ser Asn Leu Arg Pro Phe Thr Leu Tyr
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Arg Ile Asp Ile His Ser Cys Asn His Glu Ala Glu Lys Leu Gly Cys
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Ser Ala Ser Asn Phe Val Phe Ala Arg Thr Met Pro Ala Glu Gly Ala
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Asp Asp Ile Pro Gly Pro Val Thr Trp Glu Pro Arg Pro Glu Asn Ser
        835                 840                 845

Ile Phe Leu Lys Trp Pro Glu Pro Glu Asn Pro Asn Gly Leu Ile Leu
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